Pretty Keen for a Protein: Development of Small Molecule Inhibitors for a Protein-Protein Interaction Domain

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Summary

Protein-protein interactions facilitate the formation of large multi-protein complexes which are integral to all biological processes. Dysregulation of these processes has been implicated in the progression of many diseases, and therefore many protein-protein interactions have been identified as potential drug targets. Development of drugs for these non-traditional targets has been slow, due to intrinsic difficulties in designing small-molecule compounds able to competitively and selectively inhibit formation of the target multi-protein complexes.

Over 200 proteins containing SH3 domains are encoded by the human genome, and many have known roles in progression of diseases including cancer, HIV, and osteoporosis. SH3 domains bind to proline-rich regions of a protein binding partner, thereby facilitating formation of multi-protein complexes involved in cell signalling. Targeting SH3 domains with small-molecule drugs is considered a considerable challenge due to the large number of structurally similar SH3 domains and the specificity of their binding interactions with protein binding partners.

Using a structure-based design approach, 2-aminoquinoline was previously identified as a small-molecule ligand for the *murine* Tec SH3 domain. Further investigations demonstrated stronger binding ligands could be achieved with extended 2-aminoquinoline structures with largely hydrophobic scaffolds.

In order to develop more effective SH3 domain inhibitors, further investigation required identification of stronger binding yet more hydrophilic and drug-like ligands. In this project, a range of novel extended 2-aminoquinoline compounds were designed based upon the strongest binding ligands identified previously. The primary investigation focused on 2-aminoquinolines with 6-position benzylpiperidine-type substituents, and incorporation of hydrophilic structures was prioritised in the design process. Investigation of the structure-activity relationship and attempted optimisation of binding interactions with the protein target was explored through modifications in the overall ligand shape. A general synthesis of the designed novel 6-substituted 2-aminoquinolines was developed using Horner-Emmons or Wittig reactions as key carbon-carbon bond-forming steps, followed by successive Buchwald-Hartwig aminations. 6-Position extended 2-aminoquinolines with biaryl substituents were also investigated, as biphenyl structures were previously shown to favourably interact with the target SH3 domain.

A secondary investigation into the development of 3-substituted 2-aminoquinolines with phenethyl-type substituents was pursued to supplement previous investigations, which had identified that these types of compounds interact favourably with the target SH3 domain. A generalisable synthetic pathway for this range of ligands using Horner-Emmons reactions was investigated.

The relative binding affinities of the novel ligands with the Tec SH3 domain was investigated using surface plasmon resonance experiments. While the binding affinities of the 3-substituted

quinoline ligands was not sufficiently strong for investigation using this assay method, several of the 6-substituted 2-aminoquinoline derivatives were found to be the strongest binding 2-aminoquinoline ligands for the Tec SH3 domain identified to date. The strongest binding ligands contained more hydrophilic structures, demonstrating that development of effective drug-like inhibitors for the SH3 domain is feasible.

The results indicated several areas for further investigation which could yield stronger binding SH3 domain ligands. Furthermore, the effectiveness of the design strategies employed in this project provides insight into the methodology and principles which may aid development of inhibitors for a vast range of challenging protein targets.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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List of Abbreviations

Boc	*tert*-Butoxycarbonyl
BTF	α,α,α-Trifluoromethylbenzene
COSY	Correlation Spectroscopy
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
FP	Fluorescence Polarisation
HMBC	Heteronuclear Multiple Bond Coherence
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
LiHMDS	Lithium bis(trimethylsilyl)amide
n-BuLi	*n*-Butyllithium
NHS	*N*-Hydroxysuccinimide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
PBS	Phosphate-buffered saline
PH	Pleckstrin homology
PPI	Protein-protein interaction
PPII	Poly-proline type II
PRP	Proline-rich peptide
PRR	Proline-rich region
ROESY	Rotating Frame Overhauser Enhanced Spectroscopy
SAR	Structure-Activity Relationship
SH2	Src Homology 2
SH3	Src Homology 3
TFA	Trifluoroacetic acid
TH	Tec homology
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane

1 Introduction

1.1 Protein-protein interactions as drug targets

Interactions between proteins to form large multi-protein complexes are integral to cellular processes. These protein-protein interactions (PPIs) govern all important cell functions including apoptosis, proliferation, growth and development, however deregulated pathways involving PPIs are implicated in the progression of many diseases.[1,2] This has led to the identification of many key PPI targets for drug development, and consequently PPI inhibitors are being developed for many therapeutic purposes.[3,4,5]

1.1.1 Challenges of PPI therapeutic design

Although the need for PPI inhibitors is well recognized, the development of small molecules to bind to the proteins encounters significant challenges due to the nature of the binding interactions. The interactions of the proteins to form multi-protein complexes do not typically occur through deep or distinct complementary binding pockets, and instead the strength and selectivity of the interactions is the result of many smaller favourable interactions over a large surface area on the exterior of the protein structures.

Traditional drug targets, such as enzyme active sites, typically contain deep binding pockets in the protein structure which can conveniently bind small molecules with a high density of functional groups facilitating a strong binding interaction. In contrast, the surfaces of proteins involved in PPIs do not generally contain distinctive features to enable strong binding interactions. The surfaces are largely hydrophobic and comparatively flat, and opportunities for hydrogen bonding or other strong polar interactions are limited and dispersed over a larger area. Instead, a small-molecule inhibitor must compete with a large protein for binding on the hydrophobic surface where there are not sufficiently strong features that can be targeted by a much smaller molecular structure.

Methods for detection of binding regions are often incapable of identifying strong features or potential binding interactions, and the development of a small-molecule drug which can interact with several binding regions while still maintaining favourable bioavailability is a further challenge. Small molecules are typically preferable from a drug design perspective, as they are more likely to have sufficient membrane permeability and resistance to hydrolysis. Compared to peptide-based drugs, small molecules are more likely to be effective and reach the intended cellular target when administered orally, which is the preferred drug delivery method.

The typical methods used to identify lead compounds for drug targets, such as high-throughput

screening of small-molecule compound libraries, have proven ineffective when applied to PPI targets.[6] Alternate methods are instead required to identify and optimise small-molecule ligands for PPI targets. Design and development of PPI inhibitors has therefore required a much more considerable investment of time and resources compared to the high-throughput methods for conventional drug targets.

1.1.2 Progress in development of ligands for PPIs

Despite the challenges and time investment required, the increasing number of PPI inhibitors in development demonstrates that it is possible for small molecules to favourably bind to these protein surfaces in at least some select instances.

In some cases a structural feature of one of the protein-protein interaction partners can be imitated by a non-peptide small molecule, thereby giving a competitive lead compound which can be further optimised and lead to a stronger binding inhibitor. The p53-MDM2 protein-protein interaction has been a well-studied target for potential anti-cancer drugs due to the known role of MDM2 in suppressing the anti-tumour activity of p53. This interaction was considered an attractive target because the binding of p53 was found to be largely mediated by three key hydrophobic residues, and therefore a non-peptide structural mimic (RG7112, Figure 1) was developed as a potential competitive inhibitor of the p53-MDM2 interaction.[7,8] RG7112 was the first MDM2 inhibitor to progress to human clinical trials, and demonstrated anti-tumour activity and suitable bioavailability when administered orally.[9]

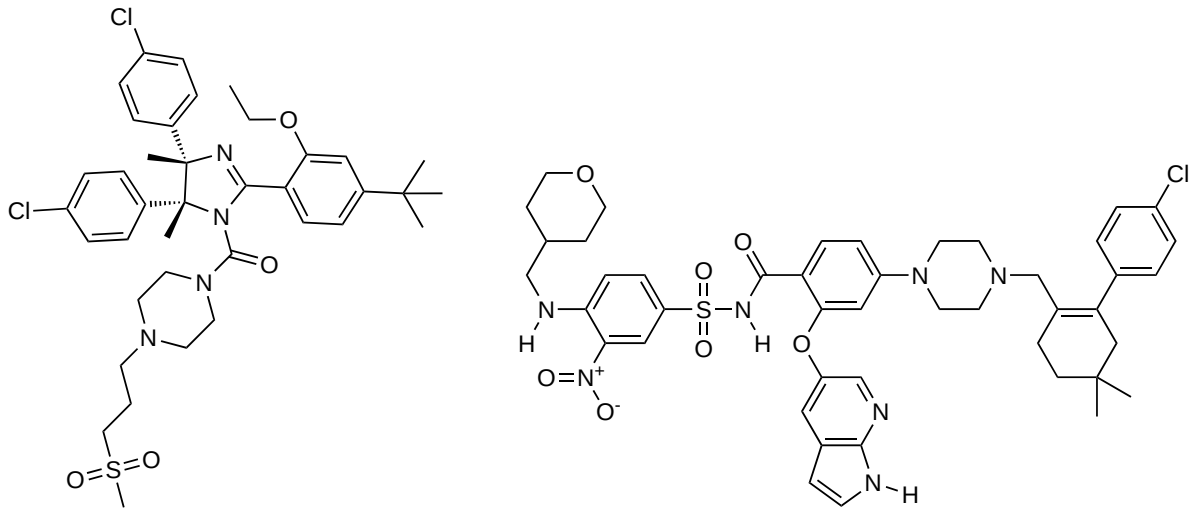


Figure 1: Small-molecule inhibitors of protein-protein interactions. RG7112: inhibitor of p53-MDM2 interaction, currently progressing though clinical trials.[7] Venetoclax: approved by the FDA in 2016 for treatment of chronic lymphocytic leukaemia, by targeting protein-protein interactions of BCL2.[10]

For many other PPI targets, however, a suitable well-defined short peptide sequence could

not be readily identified or adapted by a small non-peptide structure. In cases where the 3D structure of the protein target and the binding region are known, an alternate structure-based approach from fragment screening has been effectively utilised to design competitive small-molecule inhibitors. Venetoclax (Figure 1) was the first small-molecule PPI inhibitor designed by fragment screening to successfully progress through clinical trials and drug approval processes, and is now an orally administered medication used in the treatment of chronic lymphocytic leukaemia.[10]

Despite the success of Venetoclax and several other small-molecule PPI inhibitors currently progressing through clinical trials, the wider research and development of therapeutics targeting PPIs is still slow and challenging. The PPI inhibitors which are reaching clinical trials, however, tend to have very different structural characteristics when compared to typical small-molecule drugs. Higher molecular mass (>500 Da), largely hydrophobic scaffolds, cyclic structures, and low density of charged or polar functional groups are some of the key differences found to be characteristic of small-molecule PPI inhibitors. These characteristics reflect the structure of the target PPI binding surfaces, which are also relatively flat, hydrophobic, and lacking in well-defined structural features (such as hydrogen-bonding opportunities) which could be targeted in traditional drug design.

Based on assessment of protein-protein interaction interfaces and current development of PPI inhibitors, it has been predicted that successful compounds are required to access at least three sub-pockets on the binding surface in order to achieve a sufficient favourable binding interaction.[11] As a result, PPI inhibitors will tend to be larger structures than those targeting more traditional targets like enzyme active sites, which have more defined pockets and a higher density of potential binding interactions in one site which can be conveniently targeted by a small molecule.

The different characteristics of PPI binding surfaces means established methodologies for drug identification and development are ineffective. In cases where a competitive small-molecule mimic of the native binding partner cannot be readily developed, other methods are required to identify a lead compound. High-throughput compound screening libraries are typically used to rapidly find a lead compound for protein drug targets, but these libraries contain simple small molecules with a high density of functional groups, which are typical structures for targeting deep binding pockets in a protein structure but are not sufficient to register a binding interaction for PPI binding surfaces. Some work is progressing on developing compound libraries with larger and more structurally complex molecules specifically designed to increase the number of hit compounds identified in high-throughput screening for PPI targets, particularly taking advantage of complex and interesting natural products structures. Given the increasing number of 3D structures of protein complexes, however, a computational approach to fragment or compound screening is also becoming increasingly viable. As more PPI inhibitors are developed, the successes improve understanding of the requirements to

competitively inhibit protein-protein interactions and enable more effective inhibitor design.

1.2 SH3 domain structure and function

The SH3 domain is a non-catalytic protein domain which binds specifically to proline-rich peptide sequences of proteins to form large multi-protein complexes which are involved in many signalling pathways.[12] Signalling pathways involving SH3 domain interactions have functions including regulation of cell growth, cell proliferation and immune responses.[13] The deregulation of these signalling pathways has been implicated in the progression of diseases including cancer and osteoporosis, making many SH3 domains highly attractive targets for design of therapeutics.[14]

Proteins containing SH3 domains are very common in living organisms and SH3-like domains have also been found in bacteria, indicating the wide range of their utility in biological processes.[15,16] The 3D structures of SH3 domains are very similar due to key conserved peptide sequences or 'motifs' which dictate the overall structure and binding site (Figure 2). The human genome encodes over 200 proteins containing SH3 domains, with several containing multiple SH3 domains.[17] Many of these proteins also contain catalytic protein domains to assist in the protein's role but others, such as Grb2 and Nck, are adapter proteins which contain only non-catalytic sequences and function only to build multi-protein complexes though connections between PPI domains.[18] The Src family of kinases all contain SH3 domains which are among the most studied due to the known roles of Src kinases in disease.

	Protein	SH3 domain sequence alignment
***murine* Tec**	Tec (178-238)	NT EIVV**AMYDF**QATEA HDLRLERGQEYIIL -EKNDLH**WW**RARDK YGS-EGYI**PSNY**VT GKKS
Tec family kinases	Tec	SE EIVV**AMYDF**QAAEG HDLRLERGQEYLIL -EKNDVH**WW**RARDK YGN-EGYI**PSNY**VT GKK
	Btk	SEL KKVV**ALYDY**MPMNA NDLQLRKGDEYFIL -EESNLP**WW**RARDK NGQ-EGYI**PSNY**VT EAED
	Itk	PEE TVVI**ALYDY**QTNDP QELALRRNEEYCLL -DSSEIH**WW**RVQDR NGH-EGYV**PSSY**LV EKSP
	Txk	EEK IQVK**ALYDF**LPREP CNLALRRAEEYLIL -EKYNPH**WW**KARDR LGN-EGLI**PSNY**VT ENKI
Adapter proteins	Grb2_2	TYVQ**ALFDF**DPQED GELGFRRGDFIHVM -DNSDPM**WW**KG-AC HGQ-TGMF**PRNY**VT PVN
	Nck1_2	AY**VKFNY**MAERE DELSLIKGTKVIVM -EKCSDG**WW**RG-SY NGQ-VGWF**PSNY**VT EEGD
	Crk1_1	EEA EYVR**ALFDF**NGNDE EDLPFKKGDILRIR -DKPEEQ**WW**NAEDS EGK-RGMI**PVPY**VE KYRP
Src family kinases	Src	GGV TTFV**ALYDY**ESRTE TDLSFKKGERLQIV -NNTEGD**WW**LAHSL STGQTGYI**PSNY**VA PSDS
	Fyn	TGV TLFV**ALYDY**EARTE DDLSFHKGEKFQIL -NSSEGD**WW**EARSL TTGETGYI**PSNY**VA PVDS
	Hck	ED IIVV**ALYDY**EAIHH EDLSFQKGDQMVVL -EES-GE**WW**KARSL ATRKEGYI**PSNY**VA RVD
	Lyn	EQG DIVV**ALYPY**DGIHP DDLSFKKGEKMKVL -EEH-GE**WW**KAKSL LTKKEGFI**PSNY**VA KLNT
	Abl	NDP NLFV**ALYDF**VASGD NTLSITKGEKLRVL GYNHNGE**WC**EA-QT KNG-QGWV**PSNY**IT PVNS

Figure 2: Sequence alignment of *murine* Tec SH3 domain with selected human SH3 domains. Key conserved motifs known to be important for binding have been indicated. Alignment of sequences was assisted by SMART domain analysis tool.[19]

Although SH3 binding is known to be involved in signalling pathways for many biological processes, the roles and mechanics of the SH3 domain binding specifically are generally not

well studied or understood.[20] Identification and development of ligands for SH3 domains has been identified as a possible method for studying their roles, however due to the challenges of targeting PPIs the development of suitable inhibitors has been slow.

1.2.1 Tec family kinases

The Tec family of tyrosine kinases comprises five members — Tec, Btk, Itk, Bmx and Txk/Rlk — which are predominantly expressed in hematopoietic tissue.[21] The family of kinases have a common domain sequence, and from the N-terminus Tec kinases contain pleckstrin homology (PH) and Tec homology (TH) domains followed by the non-catalytic SH3 and SH2 domains and a catalytic kinase domain (Figure 3).[22] The presence of a PH domain is unique amongst all families of tyrosine kinases and through binding this domain facilitates localisation of the protein to the cell membrane, although Txk/Rlk does not contain a PH domain and instead binds to the cell membrane through a cysteine peptide sequence.[23] The kinases typically contain a proline-rich region adjacent to the SH3 domain, resulting in an intramolecular binding interaction which suspends the kinase in an inactive state and controls binding of the SH3 domain to other ligands.[24] The kinases generally become activated through binding to the cell membrane and phosphorylation by an Src family kinase, which potentially changes the activity of the SH3 domain and reduces the potency of the intramolecular binding interaction.[25]

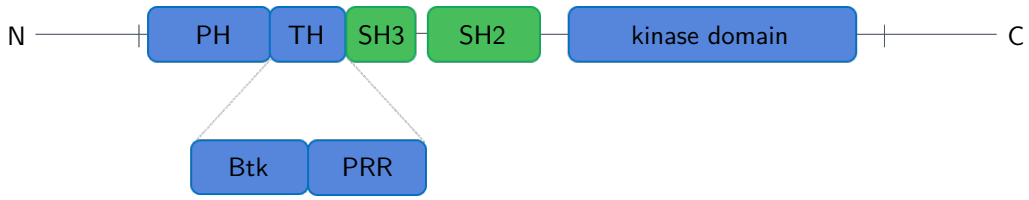


Figure 3: Representation of the domain sequence of mouse Tec protein, which is illustrative of the typical domain structure of the Tec family kinases. The TH domain contains Btk and proline-rich regions.

The Tec family of kinases are known to have involvement in signalling pathways regulating immune responses, including mediation of T-cell and B-cell activity.[25] Btk kinase is specifically involved in mediation of B-cell processes, and anticancer drugs that reduce the proliferation of B-cells by inhibiting the activity of Btk kinase have been developed.[26] Tec kinase is necessary for B-cell proliferation and can compensate for inhibition of Btk kinase, indicating that their roles have some overlap.[27] In T-cells, the Tec protein is able to bind through its SH3 domain to the proline-rich region of CD28 and thus stimulates CD28 signalling pathways which assist in full T-cell activation.[28]

Tec kinase also has an important role in inflammatory response to infection. Tec protein regulates the production of cytokines in response to fungal infection but activity of Tec kinase has no effect on response to bacterial infection.[29] Inhibition of Tec kinase in animal models

decreased the inflammatory response to fungal infections and thus dramatically reduced the mortality rate due to hyper-inflammation and fungal sepsis, indicating a potential therapeutic use of Tec inhibitors.

1.2.2 SH3 domain structure

The structure and binding of various SH3 domains has been studied using various methods including NMR spectroscopy and X-ray crystallography. While the vast majority of SH3 domain structures are yet to be fully investigated, derived structures identified to date demonstrate a high degree of structural similarity. Amongst SH3 domains there is a moderate amount of primary sequence conservation, however the core hydrophobic sequences and residues are the most conserved and lead to stability of the common SH3 domain structure. [15]

The solution structure of the *murine* Tec SH3 domain was determined using NMR spectroscopy and the overall structure is consistent with other known SH3 domains (Figure 4). [30] The *murine* Tec SH3 domain contains 60 peptide residues which form a β-barrel structure comprised of two anti-parallel, three-stranded β-sheets at right angles to each other in a formation referred to as a β-sandwich. The β-strands are connected by the RT, nSrc and distal loops and a single-turn 3_{10} helix.

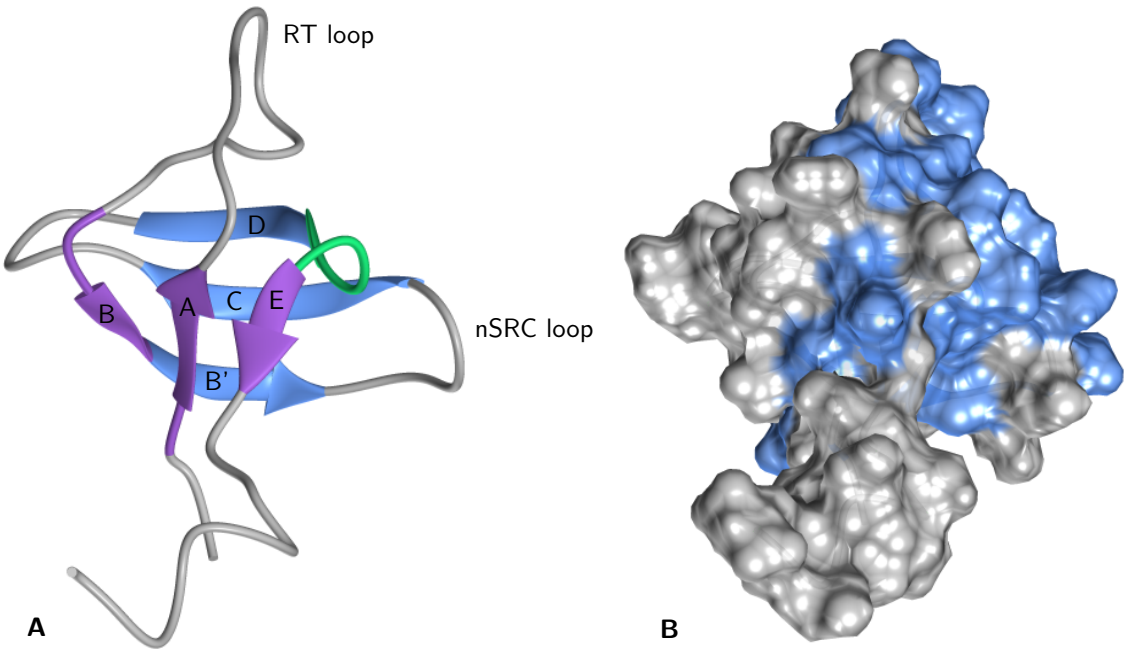


Figure 4: A: Solution structure of *murine* Tec SH3 Domain, indicating the β-strands forming the two β-sheets (indicated in purple and blue) and the 3_{10} helix (indicated in green), and B: surface representation highlighting residues found to shift upon binding to proline-rich peptide binding partner, indicating binding region (blue). PDB ID: 1GL5. [30]

The β-sandwich structure forms a hydrophobic core surrounded by conserved aromatic residues

between the RT and n-SRC loops. Studying changes in NMR shifts upon binding to a peptide ligand demonstrated that this hydrophobic surface region forms the ligand binding site. The binding site is a shallow indentation on the protein surface containing three binding pockets: the first two pockets contain highly conserved hydrophobic residues which selectively bind to proline-rich peptides, and the third pocket is surrounded by residues of the RT and nSrc loops which are less conserved and bind to charged residues of the ligand, thus establishing specificity amongst ligands.

Particular conserved sequence motifs in SH3 domains have been found to be important for interactions with ligands: the ALYDY motif in the RT loop, PXXY motif in the 3_{10} helix and the core WW motif surround the binding site and enable the selectivity for proline-rich ligands.[15] Hydrogen bonds with ligands can be formed with some residues, including the tryptophan residues and the tyrosine of the PXXY motif, which increase the strength of the binding interaction and improve selectivity. The low sequence conservation in the RT and n-Src loops surrounding these motifs in the binding site can be potentially exploited to improve the selectivity of ligands.

1.2.3 Native SH3 domain ligands

SH3 domains selectively bind to proline-rich sequences in their protein binding partners, which enables formation of the large multi-protein complexes involved in cell signalling pathways. Proteins containing a proline-rich region with two proline residues separated by two amino acid residues (referred to as the PxxP motif) are readily accommodated by the SH3 domains. These peptides form a polyproline type II (PPII) helix containing three residues per turn, which aligns the proline residues on one edge of the helix. The specificity of the interaction between SH3 domains and PxxP motifs is due to the two xP sequences aligned on one side which favourably interact with the two hydrophobic binding pockets of the SH3 domain binding site (Figure 5).[31] The proline-rich peptides are separated into two classes, each of which form a PPII helix but the two classes of ligands bind in opposite orientations depending on the position of a charged residue, usually arginine, which is identified by the third binding pocket. Class one sequences have the form [R/K]xxPxxP and class two sequences have the form PxxPx[R/K].[32]

In addition to these consensus PxxP ligands, atypical proline-containing motifs are also recognised by some SH3 domains. The protein Eps8 binds to peptides containing a PxxDY motif, and the cortacin SH3 domain binds to RxxPxxxP peptides.[33,34] In both of these cases the proline residue was found to be essential to the binding of the ligand. Some SH3 domains have also been found to bind to non-proline containing peptides or bind through hydrophobic interactions that require no particular peptide motif, for example the binding of ubiquitin to the Sla1 SH3 domain.[35]

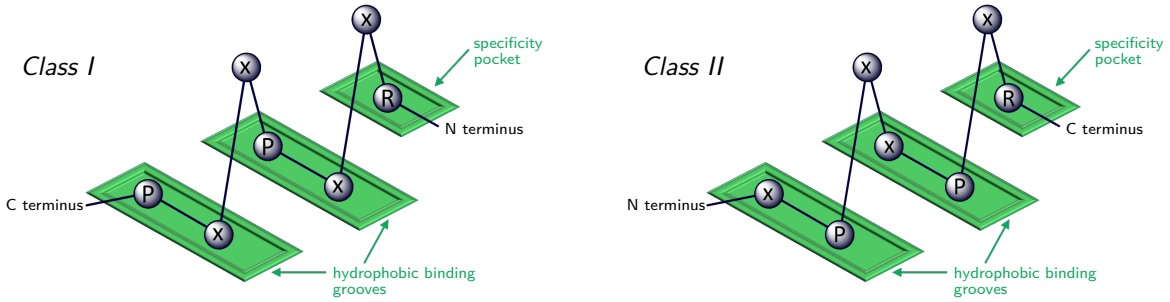


Figure 5: Binding orientations of Class I and Class II polyproline type 2 helices accommodated by shallow binding grooves of SH3 domain (shown in green). Image adapted from Mayer.[31]

Approximately 25% of human proteins contain proline-rich sequences, which provides a large array of possible ligands for SH3 domains.[36] Despite this, it has been found that SH3 domains can be very selective for a particular peptide sequence in their native environment.[36] The proline-rich region of Pbs2 protein in yeast is selective for the Sho1 SH3 domain and will not bind to any of the other 27 yeast SH3 domains.[37] SH3 domain selectivity is also found in humans despite the large number of proteins containing SH3 domains. A selective interaction and the tightest natural ligand-SH3 interaction found is between the Nef protein, which contains a proline-rich region, and the Hck SH3 domain (K_d = 130 nM), with the strong binding attributed to additional hydrophobic interactions with RT loop residues.[38] Other SH3 domains, such as in PAK2, bind to many different proteins. The binding affinity does not necessarily indicate selectivity, and most SH3 domain-peptide ligand interactions exhibit binding with moderate to weak affinity (typical dissociation constants are K_d = 1 – 200 μM) but even comparatively weak interactions can show high selectivity *in vivo*, and additional interactions outside the consensus PxxP motif improve the strength of the binding interaction.[39,40,41] Aside from sequences and favourable peptide interactions over a large surface area, other factors can also assist the selectivity of the interactions. For example, localisation of the protein may limit the number of potential partners, as Src kinases are anchored to plasma membrane and therefore only interact with other proteins in the same environment.[14]

SH3 domains are considered particularly challenging as therapeutic targets, even compared to other protein-protein interaction targets. The particular issues of developing of a selective and competitive drug-like inhibitor for a target SH3 domain is considered an intimidating prospect due to the characteristics of SH3 domains, and they have even been referred to as 'undruggable' targets.[42,43]

Competition challenge

The strength of the interactions of SH3 domains with their binding partners is due to the binding of the proline-rich peptide region with the hydrophobic binding grooves, and then further contacts with the larger binding surfaces over a large area. Effective drug compounds

need to be smaller while still making sufficient favourable binding interactions for a strong binding affinity. The SH3 domain surfaces are relatively flat and hydrophobic and don't contain close structural features which could readily be targeted by a smaller drug, due to a low density and high dispersion of any identifiable hydrogen-bonding opportunities or deeper pockets. It is therefore not considered feasible that a compound smaller than a protein or large peptide would be able to bind to an SH3 domain with a sufficiently strong binding affinity to disrupt interactions with the native binding partner proteins.

Selectivity challenge

Due to the overall conserved 3D structure and amount of sequence homology shared between SH3 domains and specifically the hydrophobic sequences forming the binding surface, the idea that a small ligand could be designed to interact selectively with only one SH3 domain is an ambitious and challenging proposition. While selectivity for SH3 domain interactions is observed in nature, this is again achieved by many small interactions over a larger surface area of the protein structures, which, so far, has not been possible to mimic with a small drug-like compound.

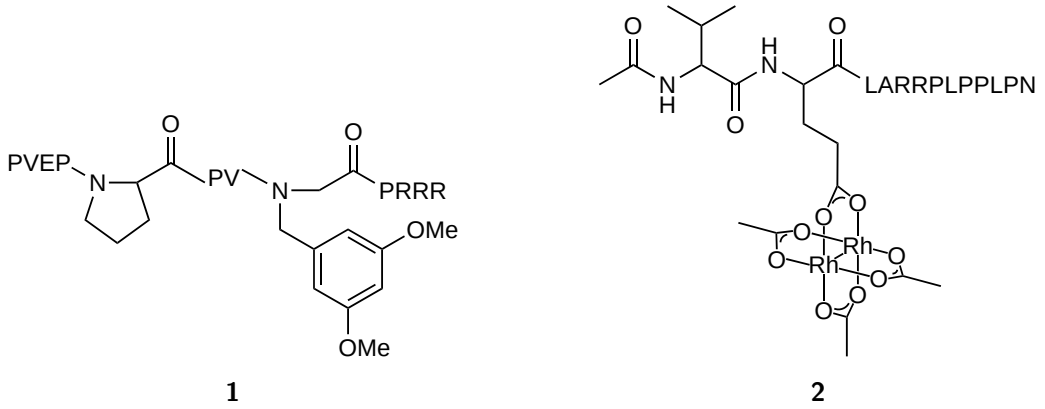
1.3 Development of ligands for SH3 domains

1.3.1 Peptide-based SH3 domain ligands

Substantial investigation and modification of peptides containing the core PxxP binding motif has been explored in order to develop more potent ligands for the SH3 domain of Src kinase. Using a combinatorial library approach, the peptide motif necessary for Src kinase binding was found to be RPLPPLP (K_d = 17.7 μM).[44] Addition of further amino acid residues VSLAR to the N-terminus of the peptide was able to target the specificity pocket and resulted in increased binding affinity compared to the core motif (K_d = 0.45 μM).[45]

Development of ligands using non-natural amino acids has given significant improvements in both binding affinity and selectivity for SH3 domains. Replacement of the proline residues of the consensus ligand motif with non-natural *N*-alkyl substituted amino acids was found to retain or improve the binding affinity of the ligands with SH3 domains, indicating that the selectivity of SH3 domains for proline-rich peptides is due to proline's unique structural characteristics as the only naturally occurring *N*-substituted amino acid.[46] Sequences containing *N*-substituted glycines mimic the backbone structure of the proline-rich peptide and the side-chains can be modified to improve the interactions with the SH3 binding site which has lead to the development of peptide-peptoid ligands with significantly stronger binding affinity. Specificity for SH3 domains could also be achieved using this approach, and a peptide-peptoid ligand (**1**) was identified which bound to the Grb2 SH3 domain with strong

binding affinity (K_d = 30 nM), and bound only weakly to Src and Crk proteins (Figure 6).[39]



1 **2**

Figure 6: Reported peptide-peptoid ligands for SH3 domains.[39,47]

Metallopeptide inhibitors derived from known peptide ligands for SH3 domains have recently been developed as more potent inhibitors with improved selectivity and biological stability compared to peptide ligands. By addition of a dirhodium core, interactions with non-conserved histidine residues near the binding site of SH3 domains can be targeted which lead to significantly stronger binding than the peptide ligands.[47] A metallopeptide ligand (**2**) was developed that bound to the Lyn SH3 domain with strong binding affinity (K_d = 6 nM) and showed weaker interactions with other Src family SH3 domains (Figure 6). Strong binding to other Src family kinases and a non-Src family kinase (Abl) SH3 domain was achieved by selective positioning of the rhodium to facilitate metal coordination to non-conserved histidine residues, showing the potential of this approach in developing targeted and possibly selective inhibitors of SH3 domains.

The development of peptide and peptide-peptoid ligands has been useful in investigation of the binding model of SH3 domains, and these ligands may achieve strong binding affinity and some specificity in their interactions, however their use as therapeutics is limited. Peptide drugs have difficulty reaching their target due to degradation by proteases and acids in the stomach if ingested, and may still be unable to cross the cell membrane if injected. Non-peptide drugs are considered more likely to be readily delivered to the target. An entirely peptoid or non-peptide SH3 domain ligand would be resistant to proteases and would be more likely to be membrane permeable, however none have yet been developed.

1.3.2 Development of Small-Molecule SH3 Ligands

While most successful inhibitors of SH3 domain interactions have been peptide or peptide-based ligands, some studies have investigated the potential of small-molecule compounds to disrupt the activity of SH3 domain containing proteins. These typically target the kinase

domain of the protein or form covalent bonds to prevent phosphorylation, rather than directly targeting the SH3 domain to prevent a binding interaction with a partner protein. The small-molecule drug UCS15A (Figure 7) was the first reported non-peptide ligand to successfully inhibit SH3 domain mediated PPIs and disrupted signalling of the Src kinase in yeast-based assays.[48] Although UCS15A was shown to disrupt the binding of the Src kinase SH3 domain to the proline-rich region of Sam68 protein, this inhibition of the protein-protein binding was subsequently determined to be due to interaction with the proline-rich binding region of the ligand rather than a direct interaction with the SH3 domain.[49]

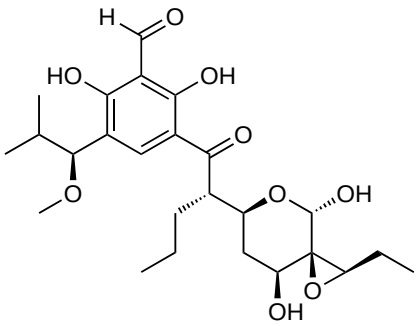


Figure 7: Structure of UCS15A, a small molecule found to regulate protein-protein interactions of the Src kinase SH3 domain with the Sam68 protein.[48]

Development of small-molecule ligands to directly target the SH3 domains of proteins would enable important investigations into the roles of proteins and PPIs in signalling pathways, and could lead to the discovery of effective therapeutics for PPIs which are currently considered 'undruggable'. Small molecule ligands for SH3 domains may also have the potential to be more selective inhibitors and have more favourable biological availability compared to the peptide-based ligands, making them more effective therapeutic compounds and more useful in biologically relevant studies.

1.4 Structure-based design of ligands for an SH3 domain

Given the current availability of structural information for many SH3 domains, structure-based ligand design is an increasingly viable option to develop higher affinity ligands that compete for the binding site. To design effective small-molecule ligands using this approach the structure solution of the target SH3 domain must be known, and the target SH3 domain and a known proline-rich peptide binding partner must be available for experimental binding and competition studies to quantitatively compare strength and efficacy of the small-molecule ligands. The *murine* Tec SH3 domain was identified as a feasible target for targeted design of small-molecule inhibitors as the solution structure of the SH3 domain was known (see Figure 4A, Section 2.2) and a suitable proline-rich peptide was known to bind to the SH3 domain and could therefore be used for competition assays.[50]

Given the structural information of the Tec SH3 domain, LUDI software was used to design small molecules which would be expected to competitively bind to the SH3 domain binding surface, at the same position as the native binding partners (Figure 8).[50] The software identifies potential favourable binding interactions on the protein target site and fits small molecular fragments to maximise the interactions, such as fragments optimising hydrogen binding opportunities and filling hydrophobic pockets with hydrophobic fragments. Proximity of these fitted fragments is then assessed, and several close fragments are chosen and then linked together into a small molecule using simple chemical linker fragments.

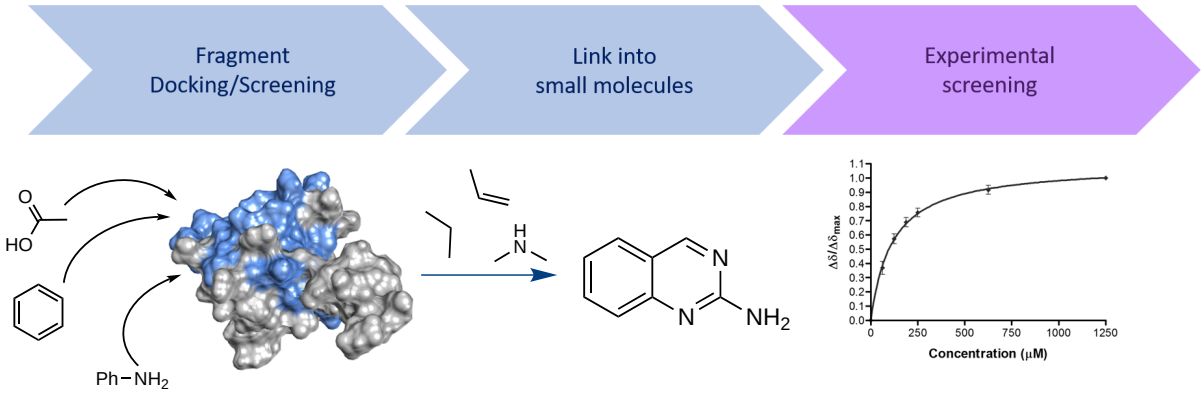


Figure 8: Fragment-based screening method using LUDI software, for identification of lead compounds predicted to bind to *murine* Tec SH3 domain.[50,51]

Of the simple compounds proposed by the software, 2-aminoquinazoline **3** was identified as a chemically suitable compound for experimental testing. This compound and a range of structurally similar compounds, including 2-aminoquinoline, were initially investigated as potential Tec SH3 domain inhibitors (Figure 9). In order to determine the lead compound an experimental assay method to measure the relative binding affinities was required.

3 **4**

Figure 9: Small molecule compounds initially investigated as potential ligands for the Tec SH3 domain.[50]

1.4.1 Measurement of relative binding affinity of ligands

Protein-Ligand Binding Assays: NMR chemical shift perturbation experiments

NMR chemical shift perturbation assays were used to determine the relative binding affinities of the potential Tec SH3 domain ligands. This assay method uses [^{1}H,^{15}N]-HSQC experiments to measure the difference in chemical shifts observed for the uniformly ^{15}N-labelled Tec SH3 domain as increasing concentrations of the small-molecule ligand are added (Figure 10).

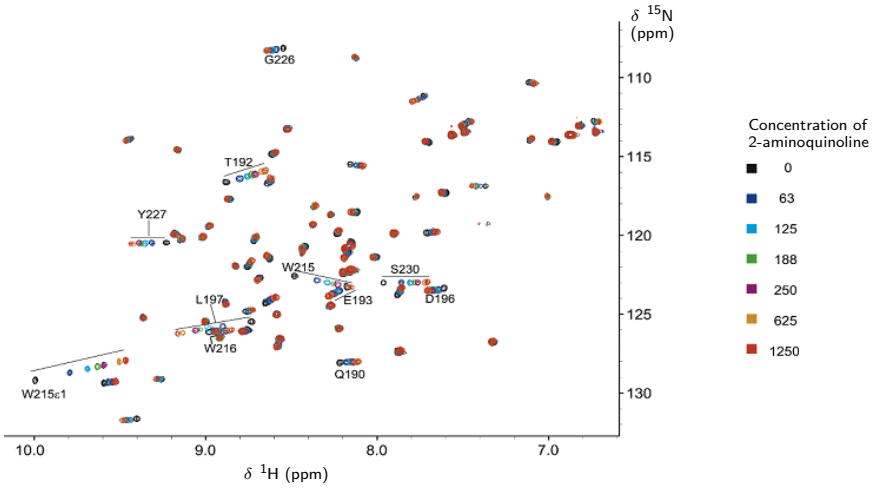


Figure 10: Example [^{1}H,^{15}N]-HSQC spectrum overlay showing shifts of binding residues in NMR chemical shift perturbation assays. Example is binding experiment of 2-aminoquinoline with Tec SH3 domain. Reprinted with permission from Inglis *et al.*, 2004.[50] Copyright 2004 American Chemical Society.

For a protein in equilibrium with its protein-ligand complex, the equilibrium dissociation binding constant, K_d, is a comparison of the dissociation rate of the complex to the rate of complex formation (Equation 1):

$$\mathrm{P} + \mathrm{L} \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} \mathrm{PL}$$

$$K_d = \frac{[\mathrm{P}][\mathrm{L}]}{[\mathrm{PL}]} \approx \frac{k_{off}}{k_{on}} \tag{1}$$

When the concentration of free protein and protein-ligand complex are equal ([P] = [PL]), then K_d is equal to the ligand concentration ([L]). From this, the K_d value referred to in this work is the ligand concentration when half the saturation binding sites of the protein are occupied, and this K_d is used as a measure of the relative binding affinity of a protein target and the ligand. The value can be compared to different complexes to determine the relative strengths of the binding interactions as a lower K_d value implies a stronger binding affinity of the protein and small-molecule ligand.

Determination of the K_d value via analysis of the [^{1}H,^{15}N]-HSQC experiments is only feasible if the ligand is in fast exchange with the protein-ligand complex on the NMR experimental timescale. If the ligand is in slow or intermediate exchange with the protein-ligand complex on the NMR timescale then the signals are broadened and the precise positions cannot be determined, and therefore the binding isotherm cannot be generated. However, if a ligand is in slow exchange with the complex, NOE build-up and transfer can occur between the ligand and protein which can be used to determine the 3D structure of the protein-ligand complex. The 3D structure would give valuable insight into the binding model of the ligand and give information which could lead to much more effective ligand design, and therefore a strongly binding small-molecule ligand which binds in slow exchange on the NMR timescale is the ultimate goal.

From the [^{1}H,^{15}N]-HSQC experiments of the ligand and labelled protein, the chemical shift difference for signals which shifted significantly upon binding (typically $\Delta\delta_H > 0.1$ ppm) was normalised and plotted against the ligand concentration to generate a binding isotherm, and determine the K_d value (Figure 11A).

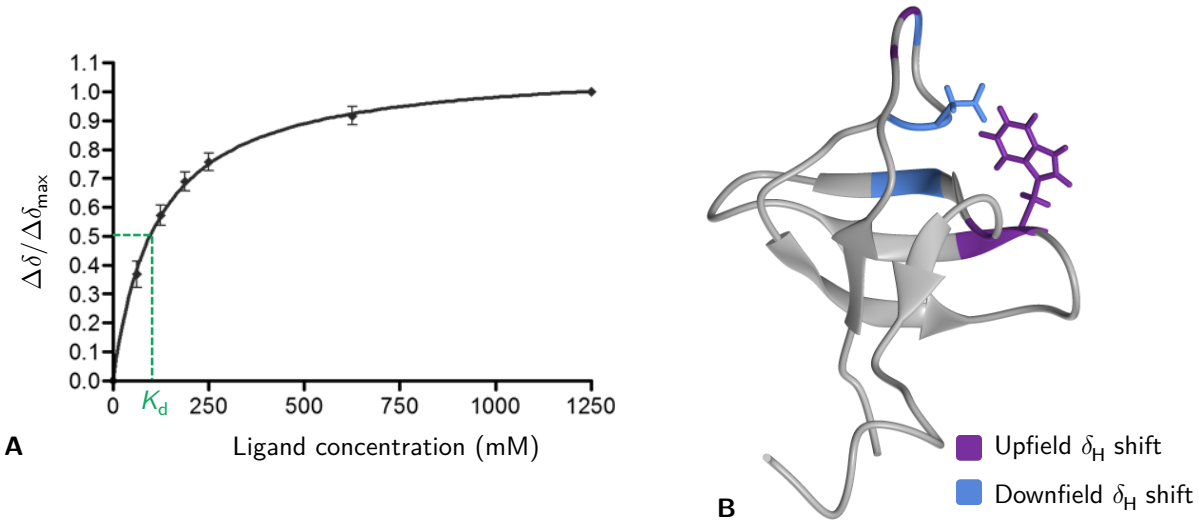
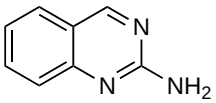
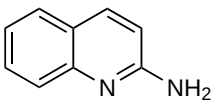


Figure 11: Example analysis of NMR chemical shift perturbation experiments. A: Binding isotherm for signficantly sifted residues upon binding to the ligand, used to determine the equilibrium dissociation binding constant, K_d. B: Mapping of shifted residues onto the Tec SH3 domain structure. Example is binding experiment of 2-aminoquinoline with Tec SH3 domain.[50]

Using the NMR chemical shift perturbation experiments, **4** was found to bind to the Tec SH3 domain with a moderate binding affinity (K_d = 125 μM), and had a stronger binding affinity than **3** (Table 1).

Table 1: Results of initial NMR chemical shift perturbation assays.[50]

	Compound	K_d
3		800 μM
4		125 μM

Further information about the position of the binding interaction can also be obtained via this assay method. Residues which have an observed change in chemical shift as the ligand is added are therefore affected by the the binding interaction and likely near the binding site, thus the key binding residues can be identified directly from the NMR spectra and mapped

onto a 3D model of the SH3 domain to give structural information of the protein-ligand complex (Figure 11B).

For both molecules similar shifted peaks were observed which corresponded to residues in the binding site specified in the LUDI ligand design, indicating both ligands bind to the same key residues as the native binding ligands and may be competitive inhibitors.

1.4.2 Investigation of 2-aminoquinoline binding model

The binding model of **4** with the Tec SH3 domain was investigated using site-directed mutagenesis experiments and analysis of the NMR chemical shift perturbation assays to assist further development of ligands.

The NMR shift perturbation experiments showed a significant upfield shift in the signal corresponding to the indole N-H of the W215 residue of the protein. This indicated there was likely a $\pi - \pi$ stacking interaction between the W215 residue and the aromatic system of **4**, and therefore the quinoline ring was important for binding of the ligand to the Tec SH3 domain.

This interaction was not sufficient to explain the moderate binding affinity of ligand **4** as other aromatic ligands had weaker binding affinity, and therefore site-directed mutagenesis studies were used to identify residues necessary in the binding site for a moderate binding affinity to be observed. These studies identified a nearby aspartic acid residue, D196, was also essential for ligand binding. It was proposed that the formation of a salt-bridge between the D196 residue and the 2-aminoquinoline core structure occurs simultaneously with the W215 $\pi - \pi$ stacking interaction, resulting in the increased overall strength of the protein-ligand binding interaction (Figure 12).

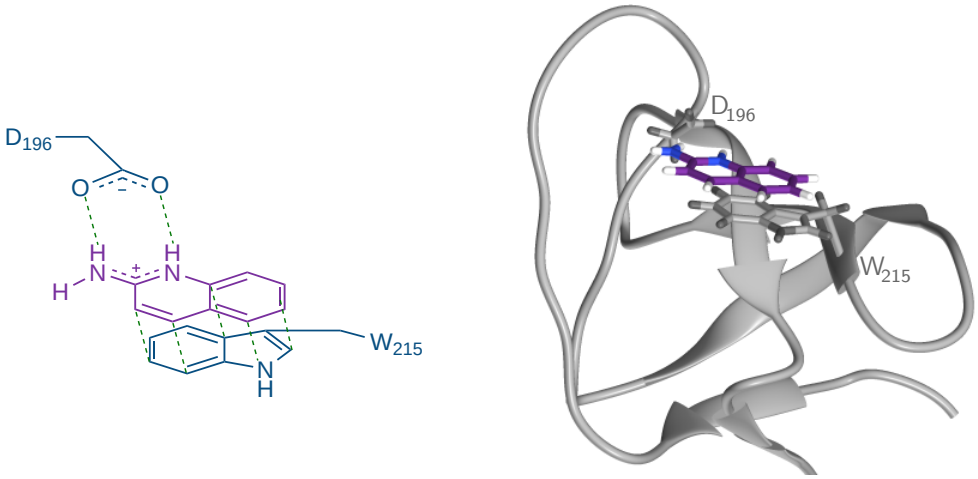


Figure 12: Proposed binding model of 2-aminoquinoline with Tec SH3 domain.[50]

These two key binding interactions result in a moderate binding affinity for ligand **4**. To

develop a ligand with a strong binding affinity additional favourable interactions with the binding surface were required and, as previously mentioned, optimisation of 3 - 5 interactions with the protein binding surface has been identified as necessary for effective PPI inhibitors discovered to date. In further development of **4** ligands for the Tec SH3 domain, further information on the binding surface can be obtained by strategically extending the ligand core with functional structures and using assay methods to determine the impact upon the binding affinity. While the exact structure of the protein-ligand binding surface cannot be determined without strong binding or slow exchange of the ligand, NMR chemical shift perturbation assays can provide information on the nature of further interactions by mapping the change in shift onto the SH3 domain structure, giving valuable information on the proximate residues which can be targeted and how the ligands can be further optimised to exploit favourable interactions.

Using the proposed binding model of **4** and the structure solution of the Tec SH3 domain, several residues near the ligand binding site were identified as possible target contacts to further improve binding of the ligand (Figure 13). It was predicted that 6-position extended 2-aminoquinolines could potentially interact with the hydrophobic L213 residue and the hydrophilic residues N211, D212 and H214. On the other side of the binding site, it was predicted that *N*-substituted 2-aminoquinolines could also make further contacts with proximate residues in the binding surface.

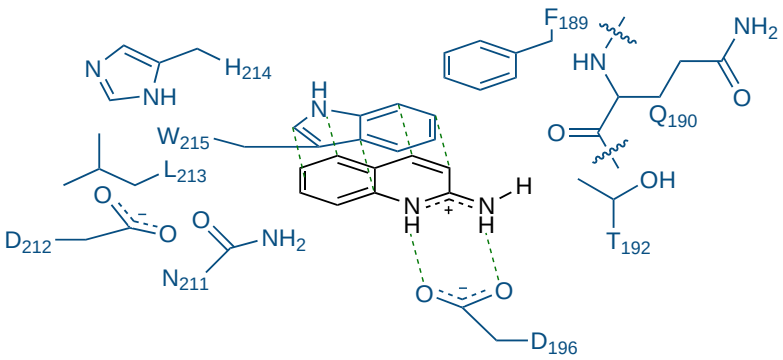


Figure 13: Proposed extended binding model of 2-aminoquinoline in Tec SH3 domain binding site, showing neighbouring residues for possible further interaction.[52]

1.4.3 Development of 2-aminoquinoline derivatives with increased binding affinity for SH3 domain

Based upon this understanding of the binding surface, a range of 2-aminoquinoline derivatives were designed, synthesised and assayed to probe the potential interactions on the binding surface. An investigation into *N*-alkylated 2-aminoquinolines indicated that these compounds bind to the SH3 domain as one of two possible rotamers, one of which is in the incorrect orientation to form a salt bridge with the aspartic acid D196 residue, and so a significant

reduction in binding affinity was observed (Figure 14).[53] *N*-Benzylated derivatives (for example **5**) recovered some of the loss in binding affinity and gave a twofold increase in binding affinity relative to the *N*-methylated derivative **6**, possibly due to an additional lipophilic interaction with the binding surface (Figure 15). None of the *N*-substituted derivatives bound with comparable binding affinity to the lead compound **4**. From these results it was determined that the essential interaction with the D196 residue was best facilitated by retaining the non-substituted 2-amino group. The identification of a potential favourable lipophilic interaction with benzyl substituents at this position was promising, but could potentially be explored further by alternate 2-aminoquinoline substituents rather than compromising optimisation of the essential salt-bridge interaction.

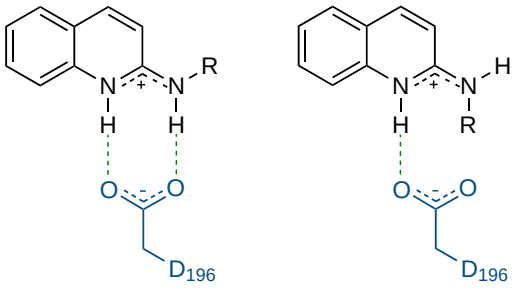
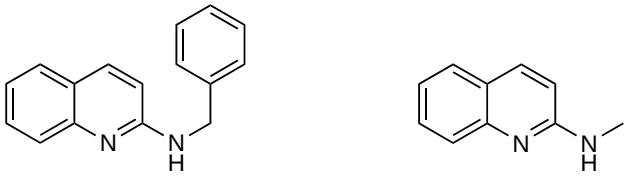


Figure 14: Proposed binding model of *N*-substituted 2-aminoquinoline derivatives with the D196 residue in Tec SH3 domain binding site, showing differing interaction of the rotamers.[50]



5
$K_d = 193\ \mu M$

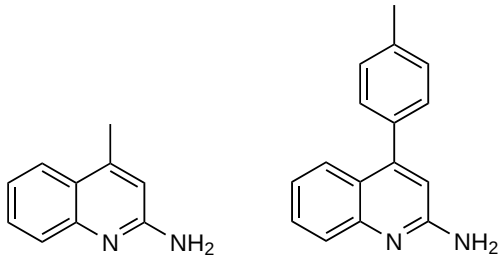
6
$K_d = 380\ \mu M$

Figure 15: *N*-Substituted-2-aminoquinoline derivatives tested for binding with the Tec SH3 domain.[53]

Substitution at each position of the quinoline ring has been investigated with varied impacts upon binding affinity. The binding affinity of 5-substituted 2-aminoquinolines was similar to that of **4** and the range of substituents tested gave no observable difference in binding interactions, which supported the model's prediction that substituents at this position are directed away from the protein binding surface and therefore make no additional contacts to improve the binding interaction.[54] One ligand was found to exhibit improved binding affinity, possibly through formation of a hydrogen bond with a nearby residue.

Introduction of a substituent at the 7-position of the 2-aminoquinoline ring was generally not tolerated in the binding site and resulted in reduced binding affinity, indicating that substituents were directed into the protein surface resulting in steric clashes which hindered the optimal interaction with key binding residues on the protein surface.[54] Similarly, addition of a

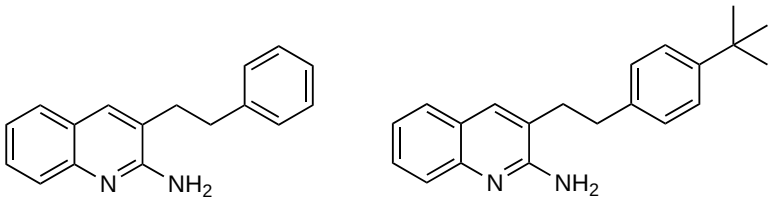
tolyl subsitutent at the 4-position was not tolerated, again potentially due to steric hindrance, although a methyl substituent enabled some improvement in binding affinity. These results indicated a small or more flexible substituent may be better tolerated and make additional favourable contacts from the 4-position of 2-aminoquinoline, although this has not been investigated further (Figure 16).[55]



7 $K_d = 65\ \mu M$ **8** $K_d = 350\ \mu M$

Figure 16: Structures of 4-substituted 2-aminoquinolines tested for binding with the Tec SH3 domain.[55]

The most significant improvements in binding affinity have been achieved by addition of substituents at the 3- and 6-positions of 2-aminoquinoline. It was postulated that substituents at the 3-position may potentially access the same interactions that gave improved binding affinity for *N*-benzylated derivatives. While addition of a phenylethyl substituent was not found to impact binding (ligand **9**), adding substituents at the *para*-position of the ring was found to improve binding. Addition of a large *t*-butyl group (ligand **10**) gave the greatest improvement in binding, likely due to favourable hydrophobic interactions with the protein surface ($K_d = 40\ \mu M$, Figure 17).[56]

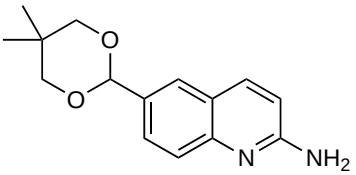


9 $K_d = 128\ \mu M$ **10** $K_d = 40\ \mu M$

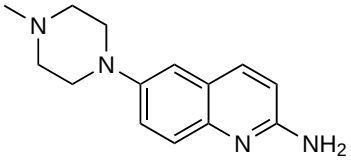
Figure 17: Structures of 3-substituted 2-aminoquinolines used to investigate additional binding interactions.[56]

Substitution at the 6-position of the 2-aminoquinoline was also found to increase contacts with the protein binding surface and improved the binding affinity relative to the lead compound **4**, giving the most successful small-molecule SH3 domains ligands to data. The 2-aminoquinoline derivative **11** with an acetal group at the 6-position of the 2-aminoquinoline showed significantly improved binding affinity (Figure 18, $K_d = 22\ \mu M$), however acetals, including

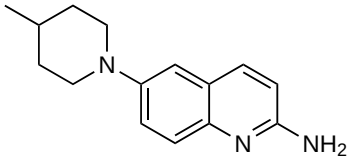
11, were shown to hydrolyse under acidic aqueous conditions and are therefore unsuitable for biologically relevant studies.[50]



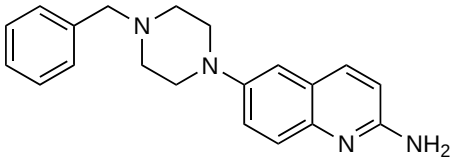
11
$K_d = 22\ \mu M$



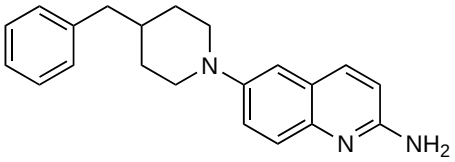
12
$K_d = 67\ \mu M$



14
$K_d = 12\ \mu M$



13
$K_d = 28\ \mu M$



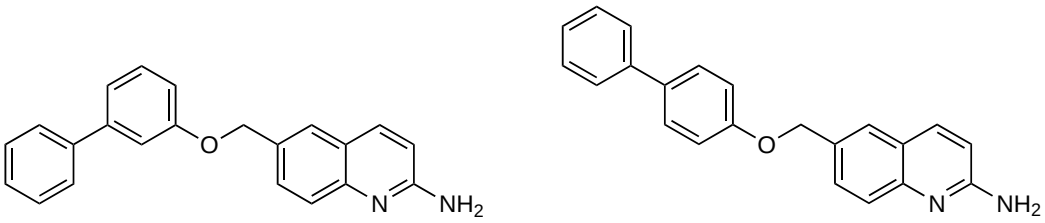
15
$K_d = 9\ \mu M$

Figure 18: Structures of 6-position heterocyclic substituted 2-aminoquinoline derivatives found to access additional binding interaction, and structure of 6-position extended 2-aminoquinoline **15**, with the strongest binding to date.[52]

To develop a ligand with better stability to optimise these favourable binding interactions, a series of 6-position heterocyclic 2-aminoquinolines were synthesised and tested for binding with the Tec SH3 domain (some results shown in Figure 18). This work identified that addition of a piperidine or piperazine substituent increased the strength of the ligand's binding interaction with the Tec SH3 domain compared to **4**, potentially by the same binding interaction as the acetal **11**. In particular, several 4-piperidine substituents were tested and observed to give lower K_d values. The best results were seen with a benzyl substituent, as with both piperidine and piperazine rings it was observed that the large substituent (ligands **13** and **15**) further improved the strength of the binding interaction over heterocycles with just a methyl group (ligands **12** and **14**, Figure 18).[52] The 2-aminoquinoline derivative **15** with a 4-benzylpiperidine substituent was the strongest binding Tec SH3 domain ligand identified. Chemical shift mapping of **15** demonstrated that additional residues were shifted in the NMR binding assay, indicating that a hydrophobic binding interaction of the benzylpiperidine substituent and the protein surface was contributing to the stronger binding interaction.

The addition of aryloxymethyl substituents at the 6-position of 2-aminoquinoline was also

investigated.[57] While these substituents showed promising results in the improvement of binding affinity for the Tec SH3 domain (comparable to the strongest binding 6-heterocyclic substituted derivatives, Figure 18), the binding interactions of the ligands with the Tec SH3 domain was demonstrably different in the NMR assays (Figure 19). Compounds **16a** and **16b** both demonstrated strong binding interactions with the SH3 domain, but the results from NMR binding assays indicated that this was due to multiple favourable binding interactions between the ligand's functional groups with the protein binding surface but that these interactions could not be simultaneously accessed. Instead, the observations indicated that the biphenyl group or the core 2-aminoquinoline structure could favourably interact with the protein surface, and the ligand alternated binding between the competing sites. It was hypothesised that the rigid structures and constrained overall shape of the molecule is hindering the ability of the ligand to optimally bind to all potential binding interactions simultaneously.



16a $K_d = 8 \pm 3\ \mu$M*

16b $K_d = 7 \pm 2\ \mu$M

Figure 19: Structures of 6-position aryloxy substituted 2-aminoquinolines found to strongly interact with the Tec SH3 domain but with atypical binding interactions.[57] ***16a** was assayed as a 7:1 mixture with **16b**.

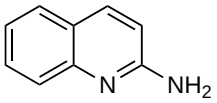
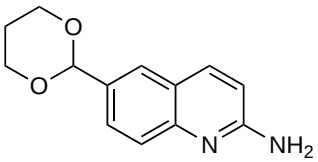
1.4.4 Progress towards selective and competitive SH3 domain inhibitors

Addition of substituents to the 2-aminoquinoline ring has resulted in significant improvements to the binding affinity for the Tec SH3 domain, and made additional favourable contacts with the protein binding surface. Some experiments were also undertaken to investigate whether these small-molecule ligands also had potential to overcome the key competition and selectivity challenges of drugging SH3 domains which have led some to call them 'undruggable' targets.

Fluorescence polarisation assays were used to investigate whether the 2-aminoquinolines could displace a proline-rich peptide from the Tec SH3 domain binding surface (Table 2)[50,53]. The concentration of lead compound **4** required to displace half of the bound proline-rich peptide from saturated Tec SH3 domain was determined to be $EC_{50} = 160 \pm 35\ \mu$M.[50] The assay results indicated that even this small compound with a moderate binding affinity would compete with a proline-rich peptide for the SH3 binding site, and also demonstrates that the small-molecule compound interacts directly with the same residues on the binding surface that would bind to a proline-rich peptide binding partner, as targeted and predicted

in the computational design of ligands. The competition assay for a 6-position extended 2-aminoquinoline derivative (**17**) demonstrated further improved results, showing that further extended 2-aminoquinolines may overcome the competition challenge and be effective competitive inhibitors of SH3 domain.

Table 2: Fluorescence polarisation competition assay results of 2-aminoquinoline and 6-position substituted 2-aminoquinoline (**17**) with the Tec SH3 domain.[50]

	Compound	EC_{50}
4		160 ± 36 μM
17		26 ± 6 μM

The other significant challenge for small-molecule inhibitors of SH3 domains is achieving selective binding to one of over 200 human proteins containing SH3 domains, which is considered particularly challenging given the highly conserved structure and sequence homology. For the 2-aminoquinoline ligands, it was known that the binding affinity is primarily due to the formation of a salt-bridge with an aspartic acid residue, and stacking with a tryptophan residue. These two residues are highly conserved amongst human SH3 domains (Figure 20).

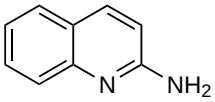
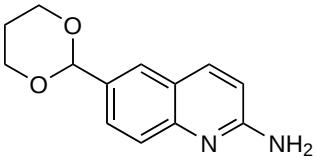
	Protein	SH3 domain sequence alignment
***murine* Tec**	Tec (178-238)	NT EIVVAMYDFQATEA HDLRLERGQEYIIL -EKNDLHWWRARDK YGS-EGYIPSNYVT GKKS
Tec family kinases	Tec	SE EIVVAMYDFQAAEG HDLRLERGQEYLIL -EKNDVHWWRARDK YGN-EGYIPSNYVT GKK
	Btk	SEL KKVVALYDYMPMNA NDLQLRKGDEYFIL -EESNLPWWRARDK NGQ-EGYIPSNYVT EAED
	Itk	PEE TVVIALYDYQTNDP QELALRRNEEYCLL -DSSEIHWWRVQDR NGH-EGYVPSSYLV EKSP
	Txk	EEK IQVKALYDFLPREP CNLALRRAEEYLIL -EKYNPHWWKARDR LGN-EGLIPSNYVT ENKI
Adapter proteins	Grb2_2	TYVQALFDFDPQED GELGFRRGDFIHVM -DNSDPMWWKG-AC HGQ-TGMFPRNYVT PVN
	Nck1_2	AYVKFNYMAERE DELSLIKGTKVIVM -EKCSDGWWRG-SY NGQ-VGWFPSNYVT EEGD
	Crk1_1	EEA EYVRALFDFNGNDE EDLPFKKGDILRIR -DKPEEQWWNAEDS EGK-RGMIPVPYVE KYRP
Src family kinases	Src	GGV TTFVALYDYESRTE TDLSFKKGERLQIV -NNTEGDWWLAHSL STGQTGYIPSNYVA PSDS
	Fyn	TGV TLFVALYDYEARTE DDLSFHKGEKFQIL -NSSEGDWWEARSL TTGETGYIPSNYVA PVDS
	Hck	ED IIVVALYDYEAIHH EDLSFQKGDQMVVL -EES-GEWWKARSL ATRKEGYIPSNYVA RVD
	Lyn	EQG DIVVALYPYDGIHP DDLSFKKGEKMKVL -EEH-GEWWKAKSL LTKKEGFIPSNYVA KLNT
	Abl	NDP NLFVALYDFVASGD NTLSITKGEKLRVL GYNHNGEWCEA-QT KNG-QGWVPSNYIT PVNS

Figure 20: Sequence alignment of *murine* Tec SH3 domain with selected human SH3 domains. The conservation of the tryptophan and aspartic acid residues known to be important for binding of 2-aminoquinoline ligands to the Tec SH3 domain has been indicated. Alignment of sequences was assisted by SMART domain analysis tool.[19]

Aside from these two residues and other highly conserved sequences (see Figure 2), there are regions with a lower degree of sequence conservation. For the 2-aminoquinoline ligands, it

would be expected that extending the structure may form additional favourable contacts with less conserved residues on the SH3 domain surface, and therefore may achieve some selectivity for the Tec SH3 domain over others. Using the fluorescence polarisation displacement assay, the binding activity of 2-aminoquinoline and the 6-position extended 2-aminoquinoline **17** with selected other human SH3 domains was investigated, and some selectivity was observed in both cases (Table 3, with sequences of the selected SH3 domains highlighted in Figure 20).

Table 3: Fluorescence polarisation competition assay results of 2-aminoquinoline and 6-position substituted 2-aminoquinoline (**17**) with several SH3 domains.[50]

	Compound	Tec EC_{50} (μM)	Nck EC_{50} (μM)	Hck EC_{50} (μM)	Fyn EC_{50} (μM)
4		160 ± 36	150 ± 30	> 1000	no activity
17		26 ± 6	> 500	-	-

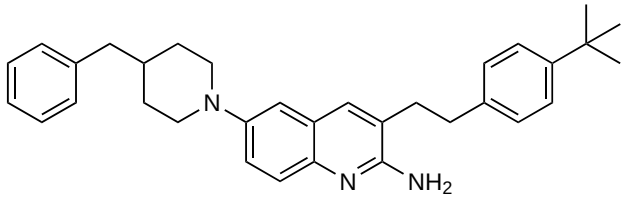
The EC_{50} value was similar for Tec and the Nck adapter protein but was diminished for Fyn and Hck, showing that even a simple ligand which binds to highly conserved residues displays some selectivity between different SH3 domains.[50] Furthermore, the 6-position extended 2-aminoquinoline ligand showed stronger binding affinity for Tec SH3 and only weak affinity for the Nck protein, which is a substantial improvement in selectivity. This effectively demonstrated that using a structure-based ligand design approach can achieve competitive and selective ligands for a protein-protein interaction surface, even for a target considered as challenging as the SH3 domain.

1.4.5 Limitations in development of SH3 domain inhibitors

Promising binding affinity improvements had been demonstrated with the extended 2-aminoquinoline derivatives, however some limitations of the ligands developed by the structure-based design approach were evident. Firstly, determining the effect of structural change upon binding affinity for the Tec SH3 domain was determined primarily by comparison of K_d values. A ligand which bound sufficiently strongly with the Tec SH3 domain surface to achieve slow exchange of protein and protein-ligand complex on the NMR timescale or to obtain a crystal structure of the protein-ligand complex had not been identified. Without determining the 3D structure of the complex the exact binding site could not be determined,

and therefore potential further interactions could not be accurately identified to assist with designing better ligands. Instead, until the structure of the complex can be determined, the progress of determining the structure-activity relationship and improving binding affinity is slower.

The other major limitation is the increasing lipophilicity of the scaffold for the stronger binding extended 2-aminoquinoline ligands. This is a common issue experienced when attempting to target a protein interaction surface, as PPI interfaces are typically flat and largely hydrophobic, and therefore favourable interactions can be made using large and hydrophobic ligand structures. One of the challenges is designing a more drug-like ligand, ideally a small molecule which has suitable water solubility to be used in biological applications. For the 2-aminoquinoline ligands for the Tec SH3 domain, significant improvements in binding affinity have been achieved be adding large and lipophilic aromatic substituents, particularly a bulky *tert*-butyl substituted phenethyl group at the 3-position (compound **10**) or a benzylpiperidine at the 6-position (compound **15**). As mentioned previously, successful PPI inhibitors typically access 3-5 favourable sub-interactions with the protein surface. Therefore, it would be expected that a compound combining these bulky substituents (such as compound **18**) could access all the favourable interactions identified to date and be a strongly binding inhibitor for the Tec SH3 domain (Figure 21).



18

Figure 21: Proposed structure which, based upon previous work, could potentially access more favourable binding interactions with the Tec SH3 domain.

Although this largely hydrophobic scaffold is highly unlikely to have sufficient water solubility to be an effective ligand for the Tec SH3 domain, it was anticipated that the incorporation of structures which access the favourable binding interactions with a less hydrophobic scaffold may be possible with some further investigation. In order to develop ligands which may access all of the identified binding interactions, improving the hydrophilicity of the substituent structures must first be achieved.

1.5 Project aims

2-Aminoquinolines have clearly demonstrated potential as SH3 domain inhibitors, but further development is required to obtain small-molecule ligands which can be used to investigate inhibition of SH3 domain-mediated PPIs and inform the structure-based development of PPIs inhibitors more generally. The primary aim of this project is to design and synthesise more effective Tec SH3 domain ligands, with a focus on compounds with stronger binding affinity for the Tec SH3 domain and improved drug-like characteristics.

The most promising ligands identified previously incorporated aromatic substituents at the 3-position or 6-position of the 2-aminoquinoline core structure. Investigating the nature of these interactions was therefore a promising avenue to develop stronger binding ligands. By strategically modifying and extending the ligand it was expected that the most favoured functional groups could be identified, and the relative orientations to simultaneously access all favourable binding interactions could be determined, thereby optimising the overall binding affinity.

It was also considered critical to explore whether less lipophilic or bulky substituents would also access these favourable interactions, as more hydrophobic scaffolds would reduce the water solubility of the compound and therefore be ineffective under biologically relevant conditions. In this work strategies will be investigated to improve water solubility while retaining overall structures which facilitate binding interactions, primarily by addition of polar functional groups and replacement of hydrophobic rings and chains with more hydrophilic structures.

Ideally, a strongly binding ligand would be achieved which would enable determination of the 3D structure of the protein-ligand complex by NMR spectroscopy or X-ray crystallography. This information would give the most accurate determination of the binding site and orientation, and would enable more efficient design of small-molecule ligands for the Tec SH3 domain. Obtaining a strongly binding ligand would give valuable information about design of SH3 ligands more generally, and open up a new array of protein interaction which could be targeted by small-molecule inhibitors.

1.5.1 Synthetic targets

2-Aminoquinoline derivatives with a 6-position benzylpiperidine substituent

6-Position substituted derivatives of **4** were the strongest binding ligands developed in previous work, with significant increases in binding affinity obtained by addition of heterocyclic substituents. A 4-benzylpiperidine substituent was the most effective as it accessed an additional hydrophobic binding interaction while maintaining the key interactions of the 2-aminoquinoline core structure. The first series of targets in this project are based upon

this ligand and aim to optimise the favourable binding interaction (Figure 22).

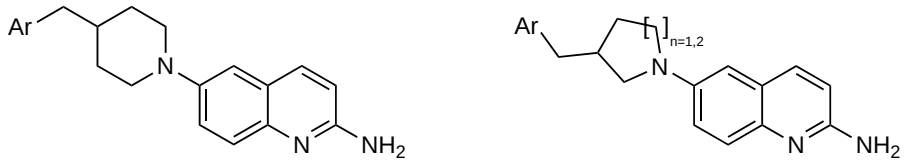


Figure 22: General structure of proposed 6-position extended 2-aminoquinoline ligands.

The nature of the interactions between the benzyl group and the protein surface will be investigated by addition of simple substituents to the benzene ring: the range of substituents will explore the effects of changing size, electronic properties and lipophilicity upon the strength of the interaction. In previous work only 4-substituted heterocycles were used, so further work in this project will investigate whether access to the binding interactions can be improved by positionally modified structures. The issue of solubility will also be investigated by addition of more hydrophilic substituents or replacement of the benzyl group with a more hydrophilic group.

The second series of target ligands were designed to further investigate the promising results from biphenyl-containing substituents at the 6-position. These compounds (**16a** and **16b**, see Figure 19) showed stronger binding interactions with the Tec SH3 domains in assays but the irregular binding results indicated the potential interactions could not be accessed simultaneously. In this work biphenyl-extended piperidine compounds were instead proposed, based upon the favourable binding interactions accessed by a 4-benzylpiperidine substituent which suggest the heterocyclic ring may better orientate the aromatic group to access the binding interaction relative to the quinoline core structure (Figure 23).

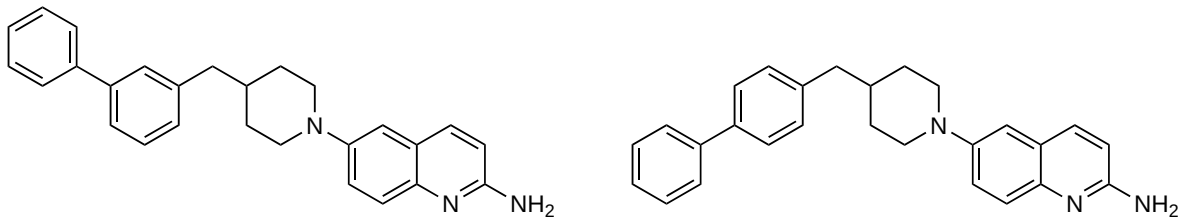
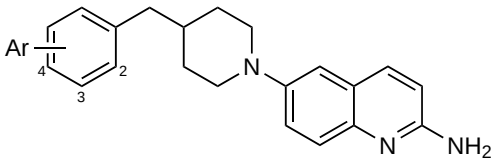


Figure 23: Structures of proposed 6-position extended 2-aminoquinoline ligands with biphenyl structures.

While the biphenyl structures are significantly hydrophobic in nature, a series of biaryls containing more hydrophilic rings were also proposed to determine if the overall hydrophobicity of the ligand can be reduced while accessing the favourable binding interactions with the largely hydrophobic protein binding surface (Figure 24).



Ar = pyridinyl, pyrimidinyl

Figure 24: General structure of proposed 6-position extended 2-aminoquinoline ligands with biaryl structures.

2-Aminoquinoline derivatives with a 3-position substituent

The hydrophobic interaction identified with 3-position extended 2-aminoquinolines had previously been favourably accessed with a large substituted phenethyl group. The best ligand had a bulky lipophilic *para*-*t*-butyl group on the benzene ring (Ligand **10**), however this is a very unfavourable structure in a small-molecule inhibitor due to the overall hydrophobicity which reduces the aqueous solubility of the compound. The replacement of the *tert*-butyl substituted benzene ring with less lipophilic heteroaromatic groups was instead proposed in an attempt to reduce the increasingly hydrophobic ligand structure while still accessing the favourable binding interaction (Figure 25).

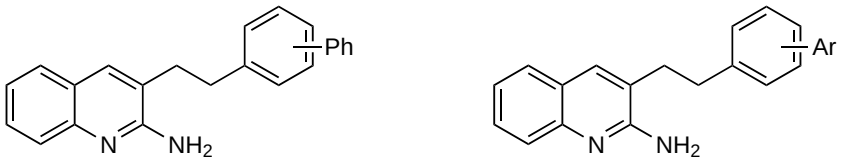


Figure 25: General structure of proposed 3-position extended 2-aminoquinoline ligands with biaryl structures.

Simpler 3-position extended 2-aminoquinolines may also be expected to improve the strength of the binding interaction, or to assist identifying structures which reduce the hydrophobicity of the scaffold and improve water solubility without compromising binding affinity. Only a small range of phenethyl groups with alkyl or fluoro substituents were investigated in previous work, and therefore alternate hydrophilic substituents were also proposed as targets to expand upon the SAR data for this library of compounds (Figure 26). Target 2-aminoquinolines to investigate the replacement of the phenethyl substituent with a pyridinylethyl substituent were also proposed to determine the effect of a change in electron density and lipophilicity of the substituent upon binding to the Tec SH3 domain.

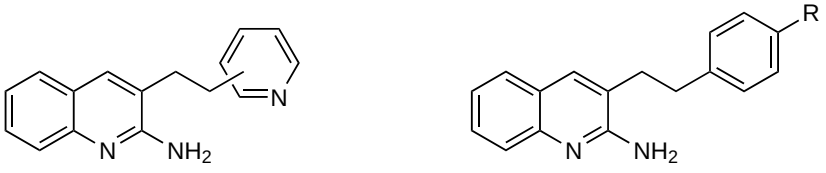


Figure 26: General structure of proposed simple 3-position extended 2-aminoquinoline ligands.

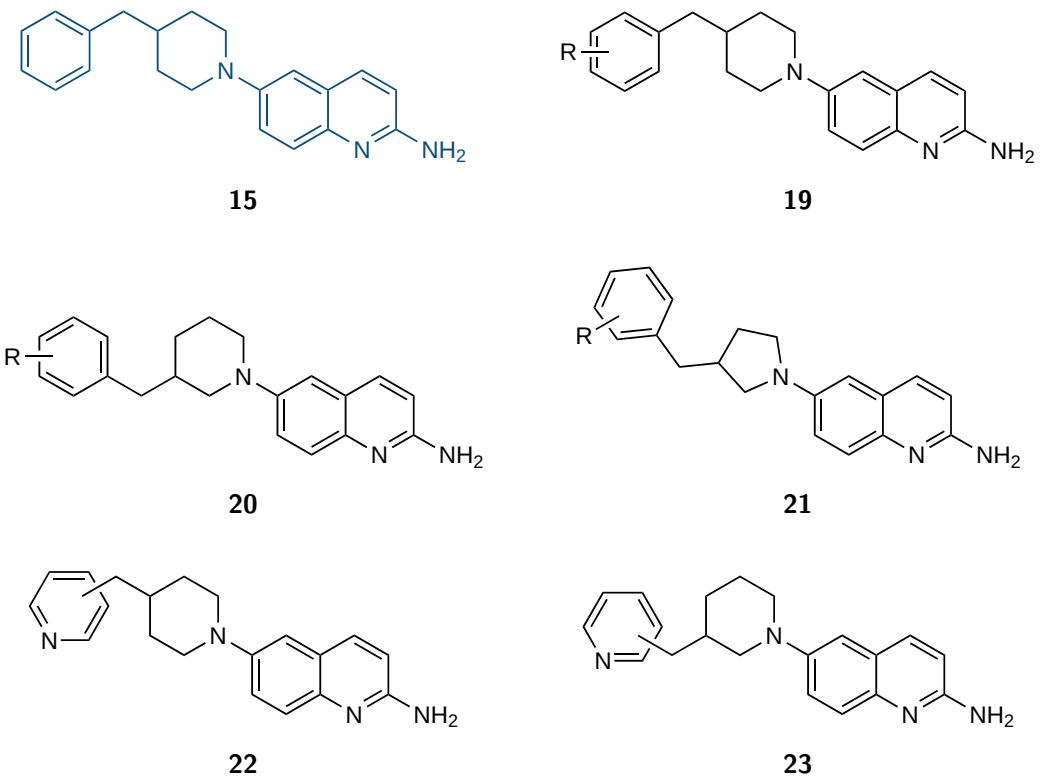
2 Synthesis of 6-position substituted 2-aminoquinolines

2.1 Introduction

Previous work into development of 6-position heterocyclic substituted 2-aminoquinolines as Tec SH3 domain ligands identified that addition of a piperidine substituent improved the binding affinity relative to the 2-aminoquinoline lead compound.[52] Further extension of the ligand with a benzyl group again resulted in an improved binding affinity to give the strongest binding ligand to date (Ligand **15**, see Figure 18), and it was proposed the improvement is a result of the benzyl group interacting favourably with an additional hydrophobic binding site on the protein surface. Further work is required to investigate the nature of this binding interaction on the protein surface and to determine whether alternative compounds similar to **15** would improve upon the binding affinity. As the 3D structure of a protein-ligand complex could not be definitively determined from any previously made 2-aminoquinoline ligand, exploration of the binding surface is best achieved by measuring changes in the binding affinity to the Tec SH3 domain with a series of structurally similar 2-aminoquinoline compounds.

It was proposed that a range of 2-aminoquinolines with benzylpiperidine-type substituents appended at the 6-position could be used to gain further information about the nature and relative position of the additional binding interaction on the Tec SH3 domain binding surface, and potentially give a strong binding ligand which could then ultimately be used to unambiguously determine the 3D structure of the protein-ligand complex. The range of derivatives investigated in this work (Figure 27) were designed to investigate the effects of adding substituents to the benzyl group (**19**) and changing the position of the benzene ring relative to the 2-aminoquinoline ligand core (**20** and **21**). In addition, a limitation identified in previous work was the relatively poor solubility of the 6-position extended 2-aminoquinoline derivatives in the aqueous conditions required for binding assays, and therefore investigation into the replacement of the benzyl group with pyridine variants was also undertaken to investigate the effect on binding and the potential for improved solubility (**22** and **23**).

For the benzylpiperidine targets, a range of simple benzyl substituents were chosen to explore the impact of various small structural changes. The functional groups range from bulky lipophilic groups (**a**) to smaller methyl substituents (**b**-**d**) and fluoro-substituents (**h**-**j**) to determine the sizes and positions of extended ligands which can be tolerated at this site on the binding surface. Adding bulky lipophilic substituents, like *tert*-butyl groups, is not preferable from a drug development perspective because it is likely to cause further issues with ligand solubility, however as PPI binding surfaces are generally largely hydrophobic these have potential from an exploratory perspective as lipophilic substituents will likely interact more strongly with the protein surface. The chosen substituents also have varying electronic



R =	**a:** 4-*t*-butyl	**b:** 2-CH_3	**e:** 2-OCH_3	**h:** 2-F	**k:** 2-Br	**n:** 2-CF_3	**q:** 2-CN
		c: 3-CH_3	**f:** 3-OCH_3	**i:** 3-F	**l:** 3-Br	**o:** 3-CF_3	**r:** 3-CN
		d: 4-CH_3	**g:** 4-OCH_3	**j:** 4-F	**m:** 4-Br	**p:** 4-CF_3	**s:** 4-CN

Figure 27: Lead compound (**15**) identified by previous studies to bind to the Tec SH3 domain,[52] and key series of 6-position substituted 2-aminoquinoline ligands proposed to investigate hydrophobic binding interaction accessed by **15**.

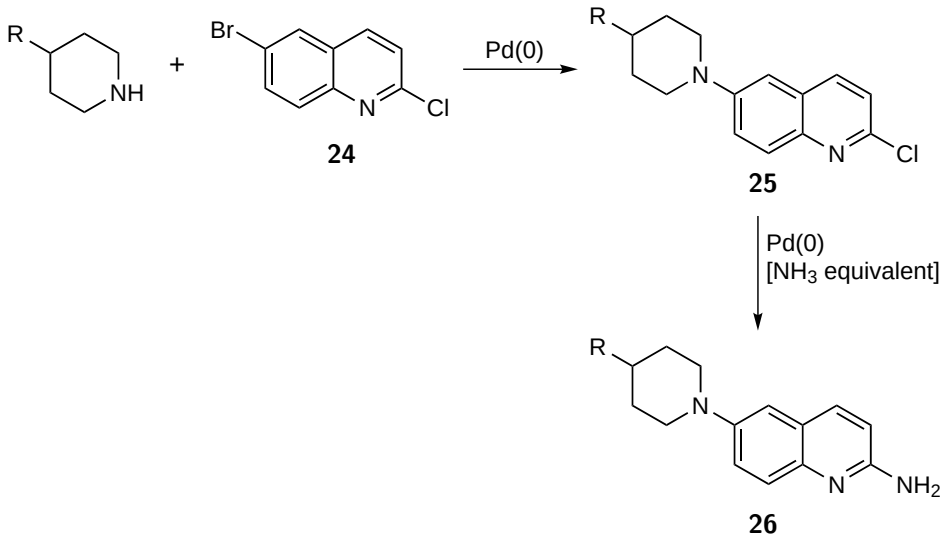
effects, to determine how the electron density in the ring impacts the binding interaction: both electron-donating substituents (including methoxy-substituted derivatives **e**-**g**), and electron withdrawing substituents (including trifluoromethyl groups **n**-**p** and nitrile derivatives **q**-**s**) were proposed as useful targets.

The bromo-substituted derivatives **k**-**m** would also be useful targets to compare with the small fluoro-substituents. In addition, aryl bromides are useful intermediates which could be further functionalised to introduce more complex substituted aromatic structures (see Chapter 3).

2.2 General synthetic pathway

The synthesis of 6-position heterocyclic-substituted 2-aminoquinolines has been thoroughly investigated in previous work, where the development of a pathway involving successive palladium-catalysed Buchwald-Hartwig aminations proved to be the most effective method.[52] In this procedure, piperidine derivatives were coupled with 6-bromo-2-chloroquinoline (**24**)

selectively at the 6-position in the presence of the 2-position activated aryl chloride bond, enabling another amine source to react at the 2-position to give the 2-aminoquinoline derivatives required (Scheme 1).



Scheme 1: Reported synthesis of 6-position heterocyclic 2-aminoquinoline derivatives by successive Buchwald-Hartwig aminations.[52]

For the first Buchwald-Hartwig amination, it was initially found that the results of the amination reaction varied significantly for different piperidine reagents and with different reaction conditions, and in some cases a range of minor products were also isolated in small quantities or observed in trace amounts (compounds **27**-**30**, Figure 28).[52]

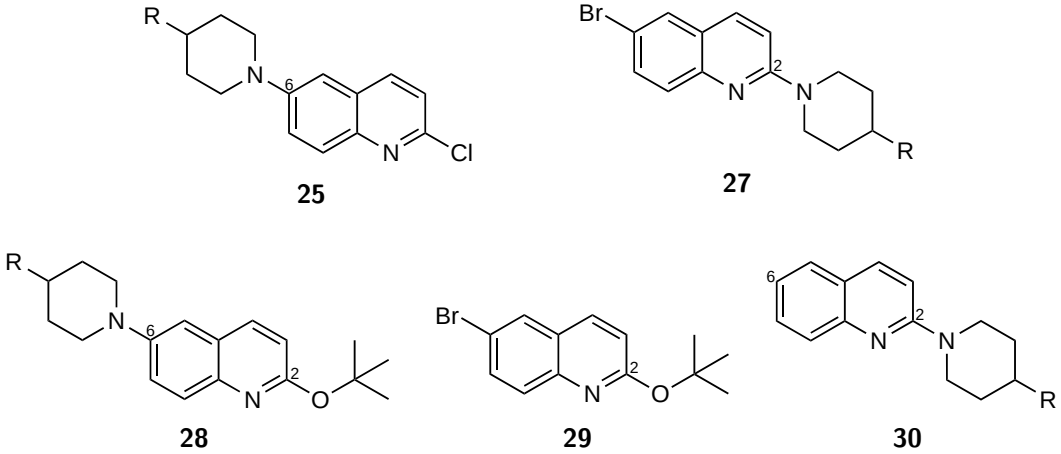


Figure 28: Potential products obtained from Buchwald-Hartwig coupling reactions of quinoline **24** and piperidine reagents.[52]

The predominant side-product observed was the 6-bromoquinoline product **27** due to the competing amination reaction with the aryl chloride at the 2-position of the quinoline, which is activated due to the neighbouring quinoline nitrogen. Other minor side-products were the result of substitution of the *tert*-butoxide base at the 2-position (**28** and **29**), and loss

of the 6-position aryl bromide under the relatively harsh reaction conditions which require high temperatures and increased pressure (**30**). The Buchwald-Hartwig catalyst system and reaction conditions for the selective amination were subsequently optimised, and yielded predominately or exclusively the target 6-position substituted 2-chloroquinoline products for a range of piperidine reagents (compound **25**).[52]

Following isolation of the target 2-chloroquinoline derivatives, several methods were investigated to convert the 2-chloroquinolines to 2-aminoquinolines (**26**), and the most effective method was determined to be a second palladium catalysed Buchwald-Hartwig amination.[52] For the synthesis of the 6-heterocyclic target compounds, the same successive Buchwald-Hartwig amination method was expected to effectively yield the desired 6-position substituted 2-aminoquinolines from **24** and the corresponding range of benzylpiperidine derivatives (Figure 29).

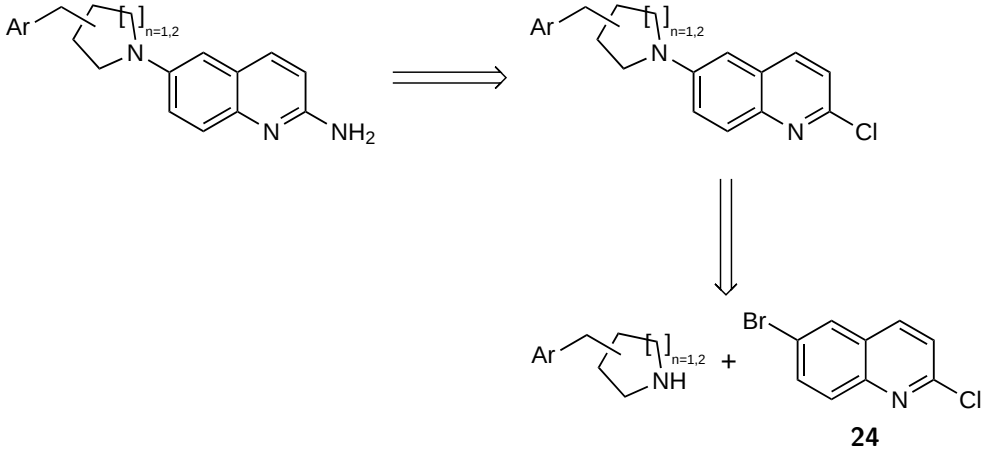


Figure 29: Proposed retrosynthesis of 2-aminoquinoline derivatives with a 6-position benzylpiperidine substituent based on previous work.[52]

By this method, the benzylpiperidine-type substituents needed to first be prepared before coupling to the quinoline (Figure 30). 4-Benzylpiperidines with substitution of simple groups on the benzene ring (**31**) were required to make the proposed target derivatives of **19**. To investigate the binding affinity of ligands **20** and **21** with a similar shape, 3-benzylpiperidines (**32**) and 3-benzylpyrrolidines (**33**) were required. The pyridinylmethylpiperidine structures (**34** and **35**) were also required to synthesise the target compounds **22** and **23**.

The 4-benzylpiperidine reagent used to synthesise **15** in the previous work was commercially available. The extended range of benzylpiperidine derivatives required for this work were not available commercially and therefore an effective synthesis of a range of these derivatives was required. It was also desirable that a method would be readily generalisable to make all the derivatives required. Several methods had been reported in the literature to make various 4-benzylpiperidine derivatives from commercially available starting materials, although none of the reported methods had previously been applied to the same range of target derivatives.

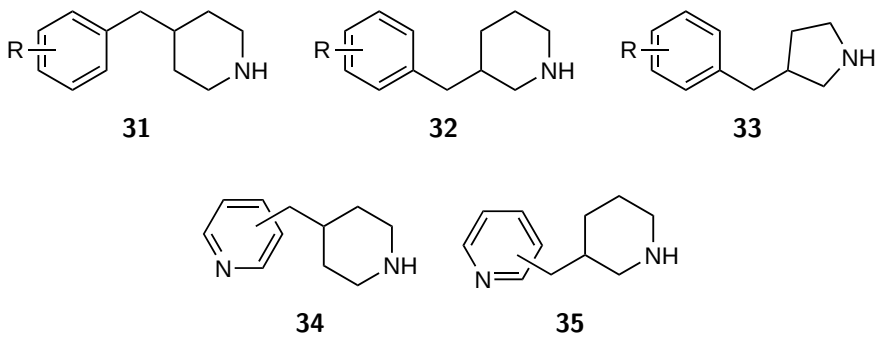
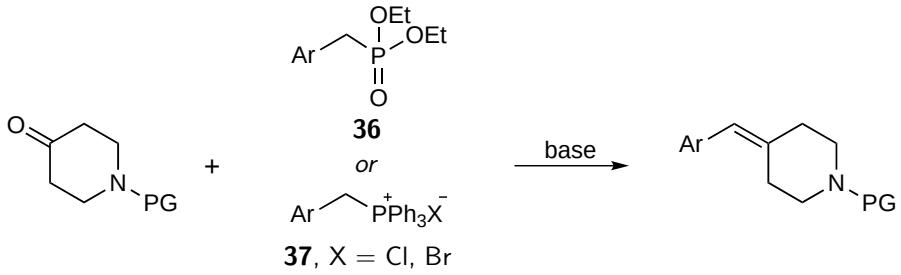


Figure 30: Range of piperidine derivatives required for synthesis of target 2-aminoquinoline ligands. For range of target R-groups see Figure 27.

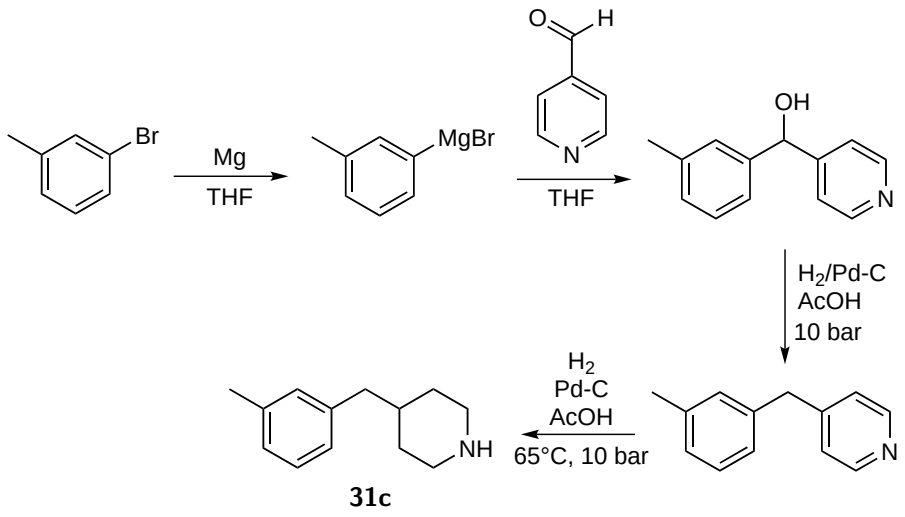
The use of a Horner-Emmons or a Wittig reaction as the key carbon-carbon bond forming step has been widely utilised in reported syntheses to make a range of 4-benzylpiperidines via a benzylidenepiperidine intermediate from a *N*-protected 4-piperidone and either a diethyl benzylphosphonate (**36**) or benzyltriphenylphosphonium salt (**37**) derivative with reasonable to high yields (Scheme 2).



Scheme 2: General synthesis of 4-benzylidenepiperidine derivatives via a Horner-Emmons or Wittig reaction. PG = protecting group.

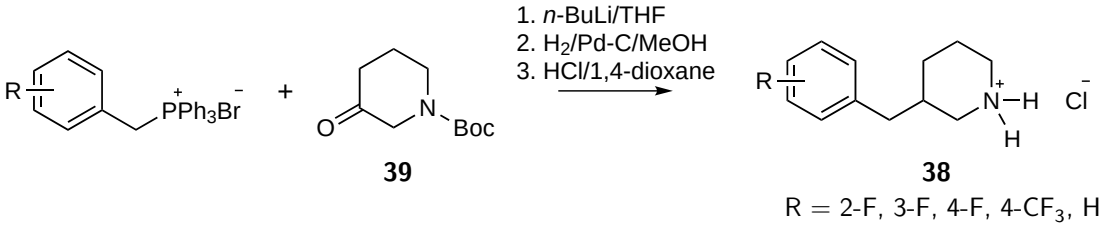
Several of the required benzylpiperidine derivatives had reportedly been synthesised via a Grignard reaction from a bromobenzene derivative and pyridine-4-carbaldehyde followed by selective hydrogenation of the pyridine ring (Scheme 3).[58] The reported yields for this process varied significantly for the range of derivatives attempted, with yields of 23-81% obtained for derivatives of **31** with methyl-, methoxy-, fluoro- or trifluoromethyl-substituents. Several different methods were required for the various derivatives and a general synthetic procedure was not found to maximise yields of all the target compounds desired in this work. Despite achieving some required derivatives in a high yield, the Grignard method was not attempted due to the lack of reliability across the reported range of compounds synthesised, which would require extensive investigation of reaction conditions for preparation of each target derivative. Instead, the reported literature processes indicated the most effective and generalisable method would be a Horner-Emmons or Wittig reaction as the key bond-forming step to synthesise **31** derivatives from a *N*-protected 4-piperidone derivative.

In this project a general synthetic method was desired, so the same method used to synthesise



Scheme 3: Example of literature synthesis of 4-benzylpiperidine derivatives by Grignard reaction.[58]

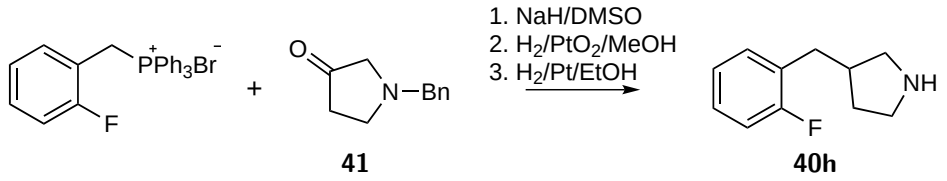
31 derivatives from a 4-piperidone would also be expected to yield **32** and **33** derivatives from *N*-protected 3-piperidone and 3-pyrrolidinone respectively. Despite the similar structure, however, a much smaller range of 3-benzylpiperidine (**32**) and 3-benzylpyrrolidine (**33**) derivatives were reported in the literature and, unlike the 4-benzylpiperidines, Horner-Emmons reactions were not a typical method used for the synthesis of the compounds. The synthesis of several 3-benzylpiperidine hydrochlorides (**38**) via a Wittig reaction had been mentioned in the literature, but as the method and results were not reported in the publications it is possible the product was not isolated and characterised (Scheme 4).[59,60]



Scheme 4: Literature reported synthesis of 3-benzylpiperidine hydrochloride derivatives via Wittig reaction.[59]

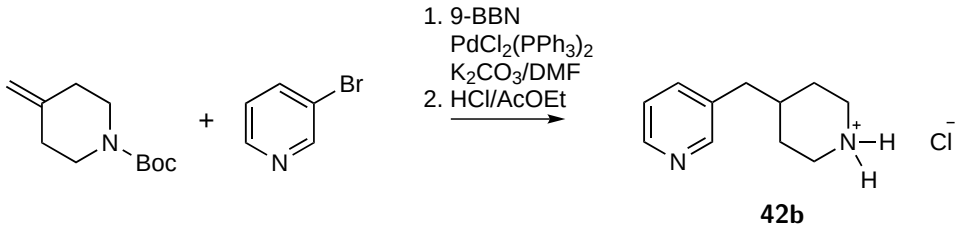
For the 3-benzylpyrrolidine derivatives only one literature synthesis via a Wittig reaction was reported, and it was noted that the yield for the 2-fluorobenzyl compound **40h** was less than the corresponding 4-benzylpiperidine derivative in the same work, although the reasons for this were not discussed (Scheme 5).[61]

Similarly, there were few reported syntheses of the desired pyridine derivatives (**34** and **35**). For the 4-piperidine derivatives, a synthesis of 2-(4-piperidinylmethyl)pyridine hydrochloride and 3-(4-piperidinylmethyl)pyridine hydrochloride (**42a** and **42b**) was reported in a 2015 patent by hydroboration with 9-borabicyclo[3.3.1]nonane (9-BBN) and palladium-catalysed cross-coupling. Although no yields or data were reported for these particular derivatives,

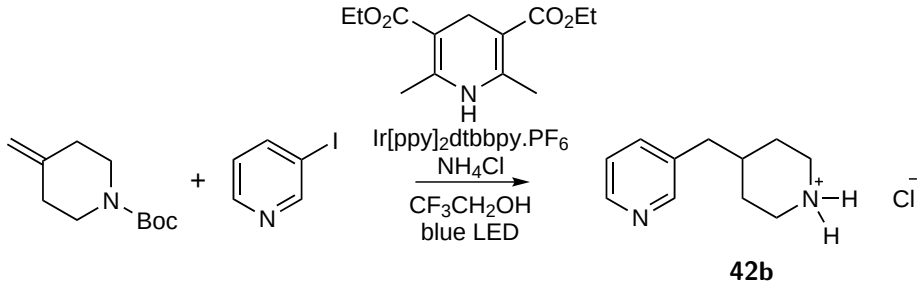


Scheme 5: Literature reported synthesis of 3-benzylpyrrolidine hydrochloride derivative **40h** via Wittig reaction.[61]

the yield of a similar compound was reported to be 46% (Scheme 6).[62] More recently, the synthesis of **42b** was achieved by a photochemical reaction through a pyridyl radical intermediate (Scheme 7).[63] The synthesis of a similar extended 3-piperidine compound **43b** has been reported previously as a four step synthesis from benzyl bromide and 2-piperidone, although again the overall yield for this process was very low compared to various syntheses of 4-benzylpiperidine derivatives (Scheme 8).[64,65]

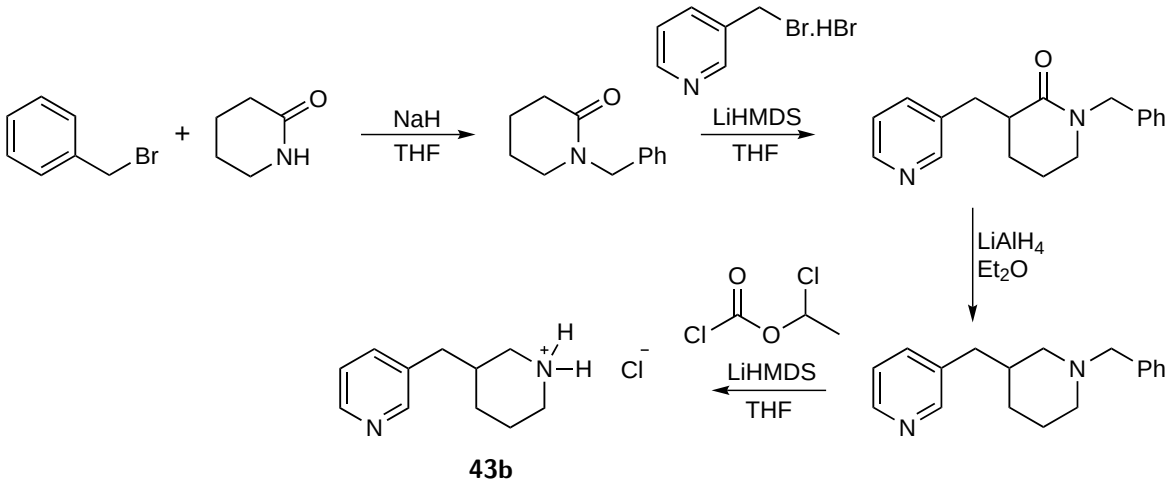


Scheme 6: Literature reported synthesis of (4-piperidinylmethyl)-pyridine hydrochloride derivatives, shown for 3-pyridine derivative **42b**.[62]



Scheme 7: Literature reported synthesis of (4-piperidinylmethyl)-pyridine hydrochloride compound **42b**.[63]

Given the availability of the required starting materials and the potential generalisability of the approach to synthesise all derivatives, it was expected that the Horner-Emmons or Wittig reactions were the most effective synthetic pathways to make the required benzylpiperidines. These methods had been applied to synthesise many derivatives of **31** previously, and it was expected the full range of required derivatives could be synthesised by either of these pathways from commercially available benzylhalides (Pathways 1 and 2, Figure 31). The Heck reaction (Pathway 3, Figure 31) was another potential method considered, although again this was less preferable because an additional carbon-carbon bond-forming reaction, usually a Wittig reaction, is required to make the methylidenepiperidine reagents. The Heck reaction could



Scheme 8: Literature reported synthesis of (3-piperidinylmethyl)-pyridine hydrochloride compound **43b**.[64]

also not be utilised to make the desired bromo-substituted derivatives due to the multiple aryl bromide bonds which would cause selectivity issues and undesired coupling reactions.

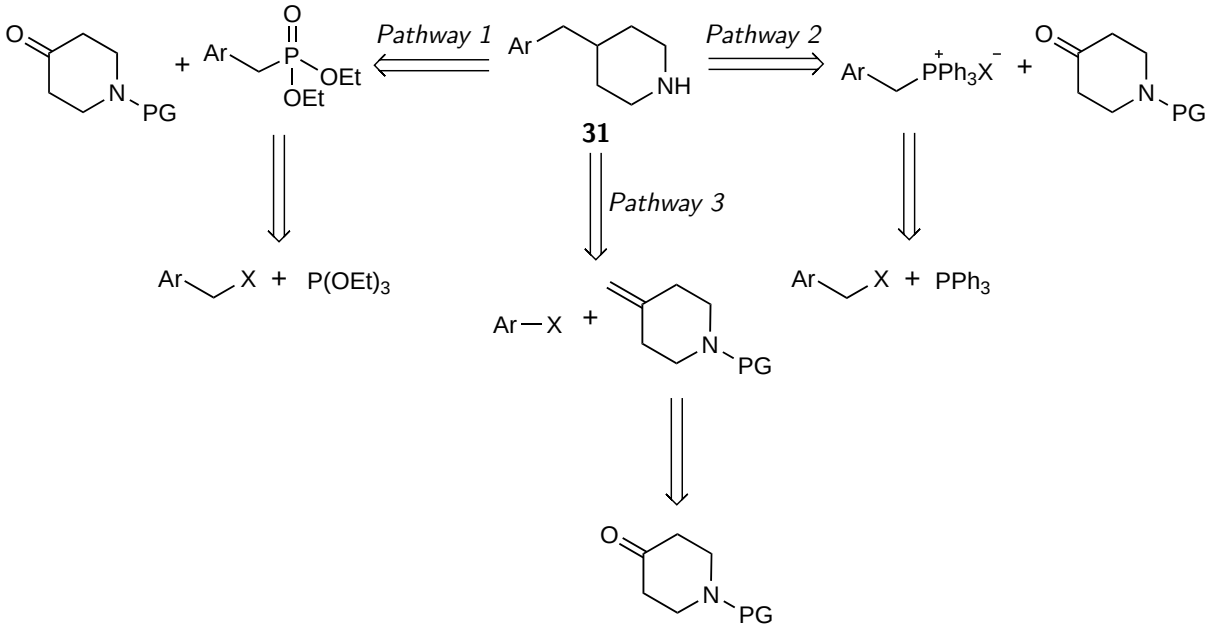
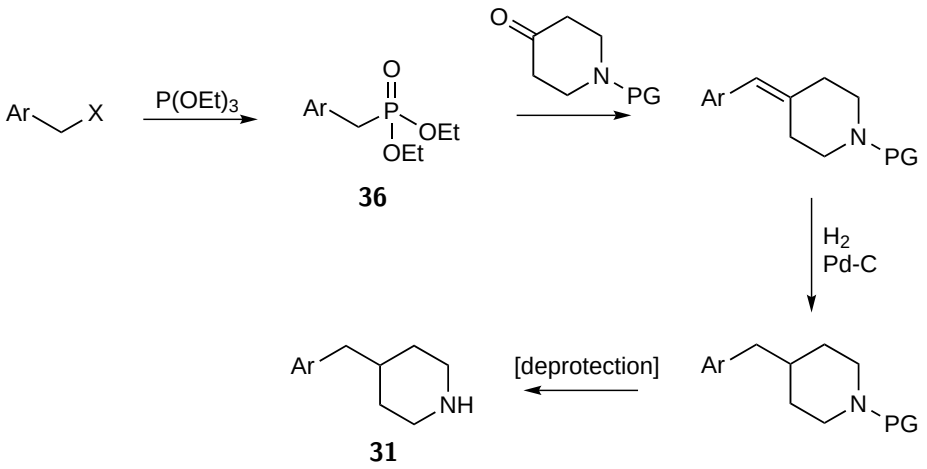


Figure 31: Potential retrosynthetic pathways for target piperidine compounds, shown for required 4-benzylpiperidine derivatives (**31**). PG = Protecting group.

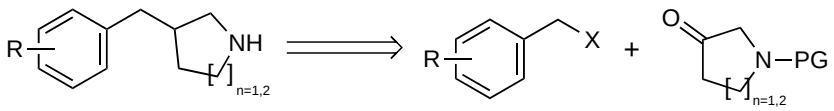
A Wittig reaction (Pathway 2) was less preferable to the Horner-Emmons reaction as the triphenylphosphine oxide by-product of the reaction is not water-soluble and therefore typically complicates purification of the alkene products, therefore the Horner-Emmons reaction pathway (Pathway 1) was the preferred method. In the proposed Horner-Emmons reaction pathway, the diethyl benzylphosphonates (**36**) would be prepared from commercially available benzylhalide derivatives and then reacted with an *N*-protected 4-piperidone via a Horner-Emmons reaction (Scheme 9). The alkene products would then be converted to the desired benzylpiperidines (**31**) via hydrogenation followed by deprotection of the amine protecting

group under standard conditions.



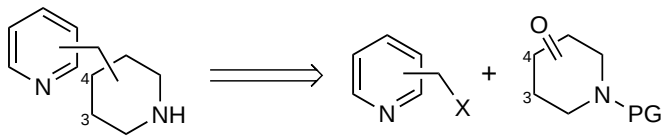
Scheme 9: Proposed general synthesis of 4-benzylpiperidine derivatives (**31**) from commercially available benzyl halides via Horner-Emmons reaction pathway.

Despite their wide utilisation in the synthesis of 4-benzylpiperidines, the Horner-Emmons and Wittig reactions had not been commonly applied in the syntheses of the other target benzylpiperidine ananlogues (**32**, **33**, **34**, and **35**). It was however anticipated that the same synthetic methods used to synthesise the 4-benzylpiperidine derivatives could then be used to synthesise the various benzylpiperidines from analogous starting materials which were also commercially available (Figures 32 and 33).



n = 2: **32**
n = 1: **33**

Figure 32: Proposed retrosynthesis of 3-benzylpiperidine and 3-benzylpyrrolidine derivatives, **32** and **33** respectively.



4-position: **34**
3-position: **35**

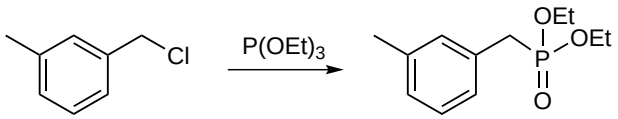
Figure 33: Proposed retrosynthesis of pyridinylmethylpiperidine derivatives **34** and **35**.

2.3 Synthesis of 2-aminoquinoline derivatives with a 6-position benzylpiperidine substituent

2.3.1 Investigation of Horner-Emmons pathway for synthesis of benzylpiperidine derivatives

Several of the required benzylpiperidine derivatives had previously been reported in the literature but were synthesised via alternate methods which could not be used to synthesise the full range of target derivatives. As an example, the methyl-substituted 4-benzylpiperidine derivative **31c** had only been synthesised via a Grignard reaction with the highest reported yield of 59% (Scheme 3).[58] However, as the Horner-Emmons reaction would be the preferable method, the attempted synthesis of **31c** via a Horner-Emmons reaction was first explored to test whether this was a suitable alternative to the literature method.

The first step in the synthetic procedure was reaction of the commercially available reagent 3-methylbenzyl chloride with triethylphosphite, which was achieved using typical Michaelis-Arbuzov reaction conditions (Scheme 10). The product was isolated by distillation with no further purification required, with quantitative yield. The spectroscopic data for the product was consistent with previously reported data, with the ^{1}H NMR spectrum showing the characteristic HP doublet at 3.11 ppm with integration corresponding to two hydrogen atoms, and the large J value for coupling with phosphorous ($^{2}J_{H,P} = 21.5$ Hz).[66]

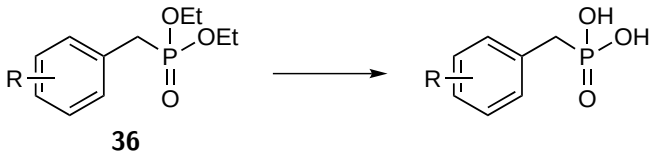


36c
100%

Scheme 10: Synthesis of diethyl 3-methylbenzylphosphonate (**36c**) via a Michaelis-Arbuzov rearrangement.

Previous work on the synthesis of similar compounds had shown typical Horner-Emmons reaction conditions with sodium hydride as the base and tetrahydrofuran as the solvent under anhydrous conditions had been most successful in yielding benzylidene products, whereas experiments with other bases and solvents had shown lower yields (unpublished work). The success of this reaction is highly dependent on the purity of the sodium hydride dispersion used as the base, the elimination of water from the reaction vessel, and rate of reaction as degradation of the sodium hydride to sodium hydroxide in the presence of water was proposed to result in hydrolysis of the benzylphosphonate reagent (Scheme 11) and therefore adversely impact the reaction yield. Both benzyl-protected and Boc-protected 4-piperidones are commercially available, however the simple and fast removal of Boc-protecting groups under acidic conditions was considered preferable to the removal of the benzyl-protecting

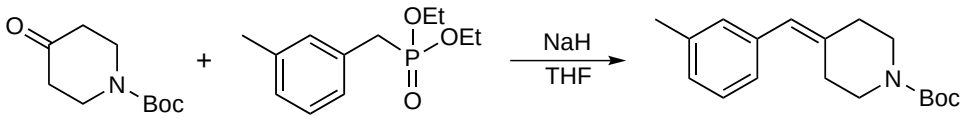
group which typically involves harsher conditions, and therefore the Boc-protected piperidone **44** was used.



36

Scheme 11: Proposed hydrolysis reaction of diethyl benzylphosphonate derivatives (**36**) due to presence of NaOH in reaction mixture.

Using these reaction conditions, diethyl 3-methylbenzylphosphonate (**36c**) was reacted with *N*-Boc-4-piperidone (**44**) and one product was formed (Scheme 12). Spectroscopic analysis of the crude mixture showed a characteristic singlet alkene signal in the ^{1}H NMR spectrum at approximately 6.3 ppm, confirming successful formation of an alkene from the Horner-Emmons reaction.



44 **36c** **45c**
87%

Scheme 12: Synthesis of Boc-protected benzylidenepiperidine **45c** via Horner-Emmons reaction.

Isolation of the product and analysis by spectroscopic methods indicated successful synthesis of the desired product **45c** with a good yield (87%). HRMS analysis of the product showed a mass peak of 232.1332 corresponding to the product with loss of the labile *t*-butyl group (expected m/z 232.1338), although the mass peak corresponding to the parent structure was not observed. Analysis of the ^{1}H NMR data for the product showed the alkene singlet signal at 6.33 ppm, and the group of four broad signals upfield of the alkene signal in the ^{1}H NMR spectrum corresponding to the hydrogens in the piperidine ring. Each of the piperidine hydrogen signals integrated for two hydrogen atoms, and the [^{1}H,^{13}C]-HSQC data demonstrated that each of these signals corresponded to a CH_2 group. This pattern would not be expected of a piperidine ring in a chair conformation, as the axial and equatorial hydrogen atoms would be in distinct environments and therefore have different ^{1}H NMR signals. In this case, however, the 4-position substituent is an alkene and therefore planar, and the Boc-protecting group also has partial double bond character (Figure 34), and therefore it is expected that the piperidine ring of **45c** is substantially planarised, leading to the lack of distinct axial and equatorial hydrogen environments for the piperidine ring.

The broadness of the signals is also indicative of the restricted conformation of the ring which results in slow ring-flipping on the NMR timescale. This broadening effect had a very significant impact upon the ^{13}C NMR spectrum, as the piperidine carbon atoms were

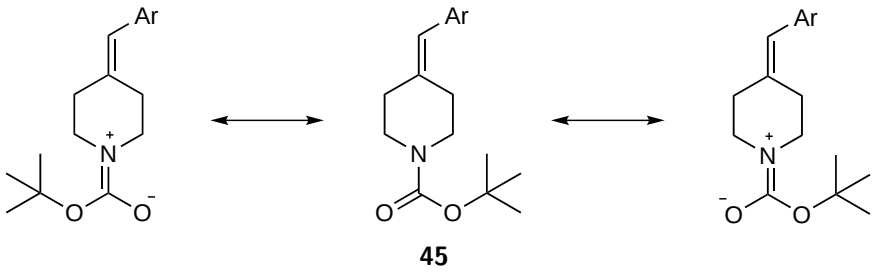


Figure 34: Structures of Boc-protected piperidines showing partial double-bond character of C-N bond.

significantly broadened and the signals for the carbons adjacent to the nitrogen atom were almost indistinguishable from the baseline of the spectrum, although the [^{1}H,^{13}C]-HSQC NMR experiment could be effectively used to definitively determine the position of the signals which appeared to coincide or overlap due to the broadness (Figure 35).

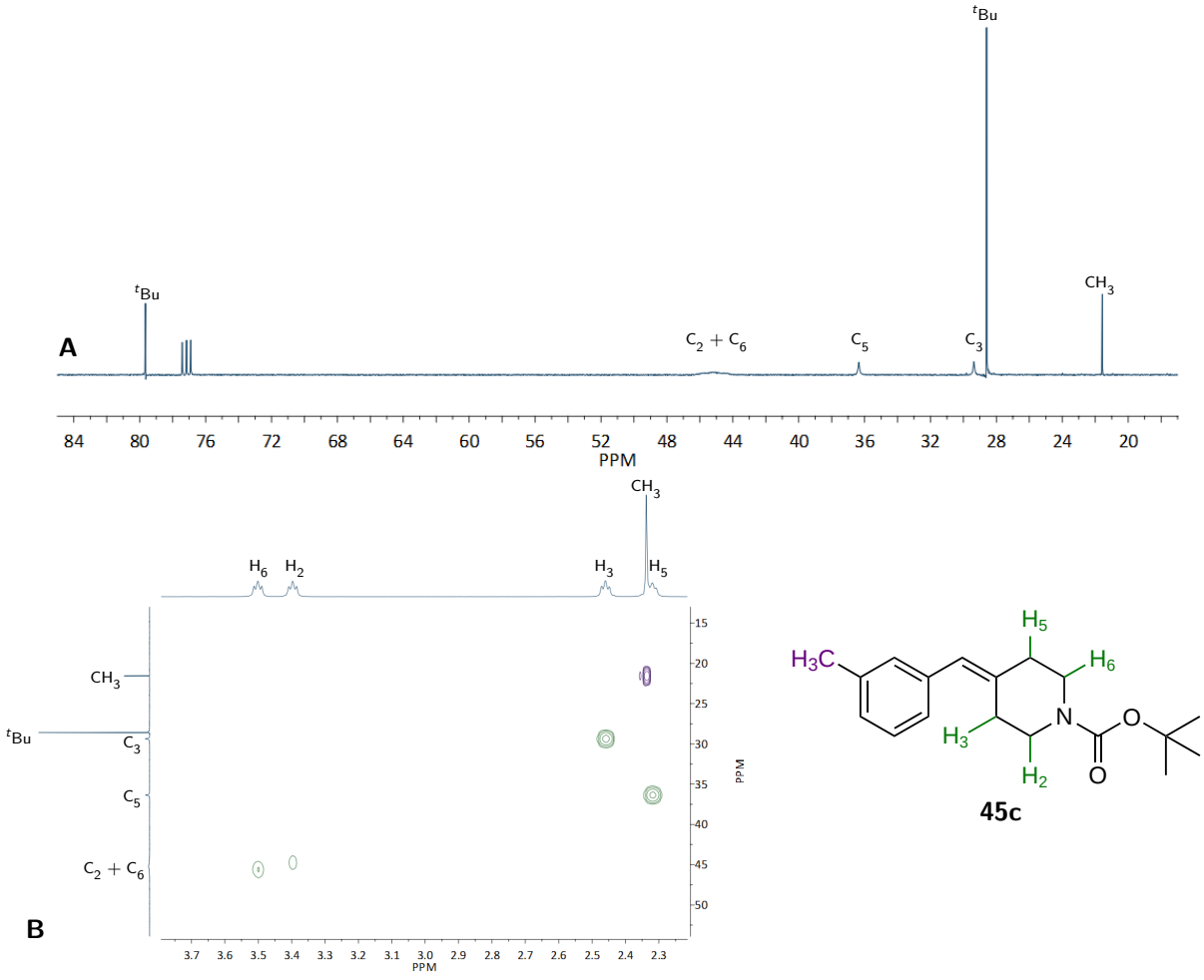


Figure 35: Example HSQC correlations used to identify broad ^{13}C NMR piperidine ring signals of Boc-protected benzylidenepiperidine derivatives. A: ^{13}C NMR spectrum of **45c** showing broadened signals, and B: DEPT-edited [^{1}H,^{13}C]-HSQC spectrum used to identify broad ^{13}C NMR piperidine ring signals of **45c**.

The piperidine ring had reduced symmetry compared to the piperidone starting material due to the asymmetrical alkene, therefore one side of the piperidine ring is in closer proximity

to the large substituted benzene ring. ROESY correlations could be used to show which signals corresponded to piperidine hydrogen atoms on the side further from the benzene ring as these hydrogens showed a ROESY correlation to the alkene hydrogen (Figure 36). The ROESY experiment indicated that the signals for piperidine hydrogen atoms adjacent to the alkene bond were shifted slightly downfield if on the same side of the alkene as the benzene substituent, showing these are slightly deshielded by the aromatic ring relative to the hydrogen atoms on the opposite side to the benzene ring.

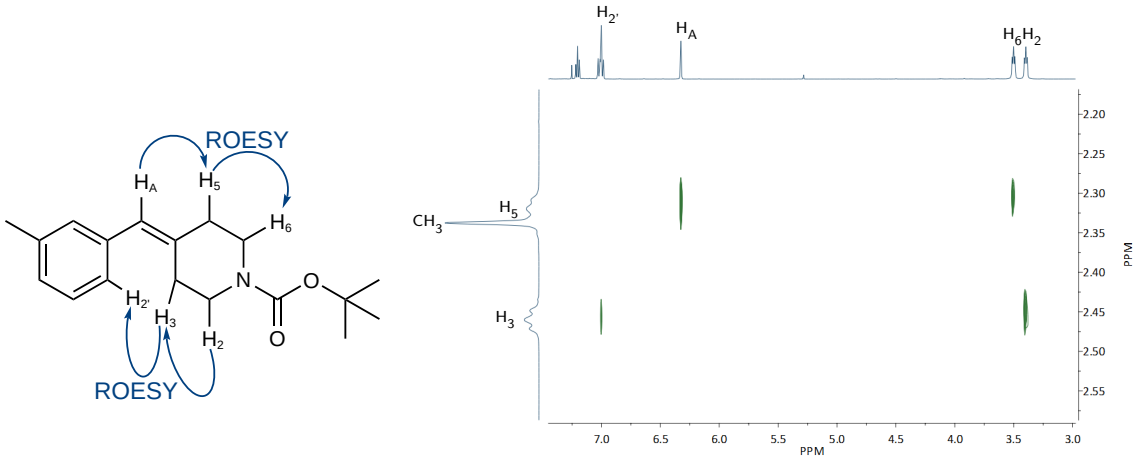
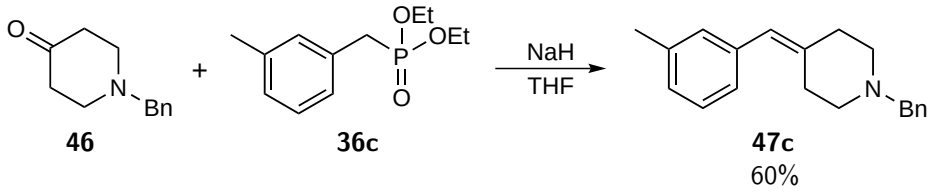
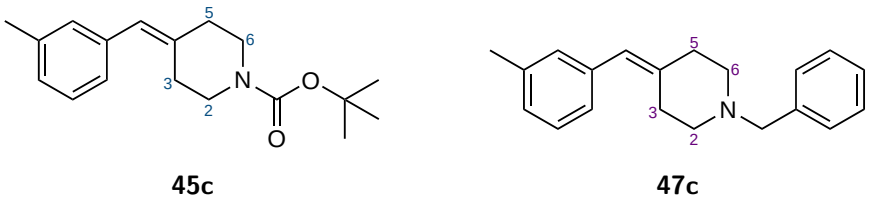


Figure 36: ROESY correlations showing assignment of asymmetric piperidine ring signals for **45c**.

Given the broadness of the signals which hinders identification and assignment of all signals, use of an alternate protecting group was investigated to ascertain whether the Boc-protecting group is affecting the piperidine ring conformation and if better clarity in the NMR spectra could be achieved for a similar compound with an amine protecting group which does not effectively planarise the piperidine the ring. The benzyl-protected piperidone reagent **46** was used and with the same Horner-Emmons reaction conditions one product was obtained (Scheme 13). The alkene signal at 6.24 ppm in the ^{1}H NMR spectrum was clearly present, indicating that the reaction had proceeded successfully to give the alkene **47c**. Piperidine ring signals very similar to that observed for **45c** were observed in the hydrogen NMR spectrum, with broad signals appearing for each CH_2 in the ring instead of the more complex pattern expected if the ring was in a chair-like conformation. Again, this indicates that the planar alkene bond is resulting in a substantially planarised ring with no distinct axial and equatorial hydrogen atoms observed in the ^{1}H NMR experiments, and therefore the planarised ring conformation proposed for the Boc-protected compound **45c** previously is not solely due to the partial double bond character of the Boc-protecting group. Because of these changes in conformation (c.f. the results from synthesis of **45c** above) the ^{13}C NMR signals for the benzyl-protected product were not also broadened and did not overlap, making the spectra simpler to interpret and enabling unambiguous assignment of all signals (Figure 37).



Scheme 13: Result of Horner-Emmons reaction with *N*-Bn-4-piperidone (**46**) and diethyl 3-methylbenzylphosphonate (**36c**).



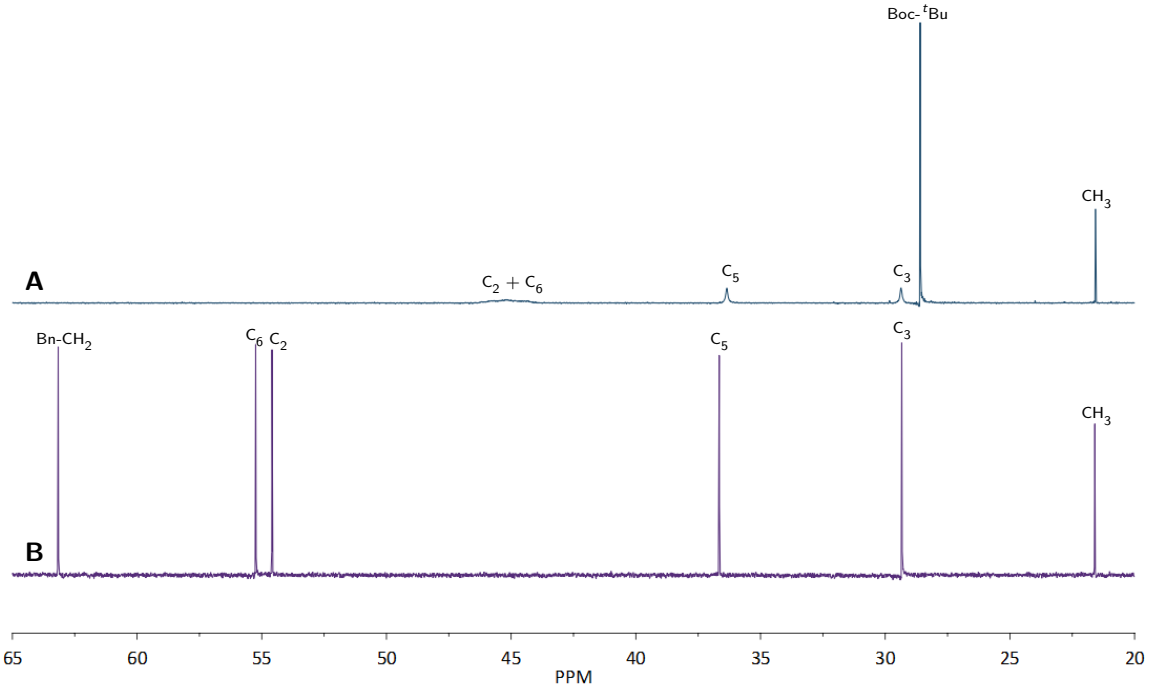
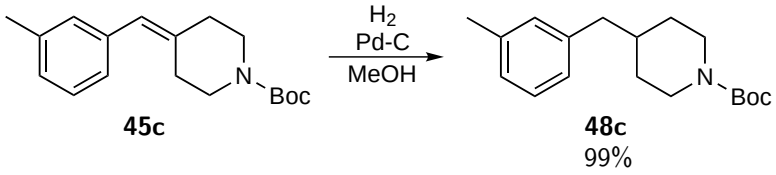


Figure 37: Comparison of ^{13}C NMR spectra of A: Boc-protected Horner-Emmons product **45c**, and B: benzyl-protected Horner-Emmons reaction product **47c**.

The difference in broadness for the ^{13}C NMR spectra of the two Horner-Emmons products was confirmation that the protecting group changes the characteristics of the piperidine ring, but aside from this key difference the spectra were directly comparable and similar. With comparison to these results from the benzyl-protected product **47c**, the evidence from the NMR data for the Boc-protected product **45c** clearly demonstrates the synthesis of **45c** was achieved, and provides evidence of the conformation of the structure and the factors influencing the conformations: the planarised piperidine ring is primarily due to the external planar alkene bond as designed, and the Boc-protecting group on the piperidine nitrogen slows the interconversion of the ring conformations. The data collected sufficiently demonstrates successful formation of the desired Boc-protected piperidine product **45c** in a high yield from

the Horner-Emmons reaction.

The Boc-protected Horner-Emmons product **45c** was reacted under standard Pd-catalysed hydrogenation conditions to give the product **48c** in almost quantitative yield (Scheme 14). The reaction was shown by NMR spectroscopy and mass spectrometry to be successful, most distinctively by the loss of the alkene signal in the ^{1}H NMR spectrum and a new signal appearing as a doublet and with integration for two hydrogen atoms, corresponding to the methylene bridge. The HRMS data showed the expected peak of 234.1491 for the product with loss of the labile *tert*-butyl group (calculated m/z 234.1494), showing successful mass increase corresponding to two hydrogen atoms as expected for a hydrogenation of one carbon-carbon double bond. In addition to the expected fragmented product peak, a comparatively small mass peak corresponding to the full molecule was observed for **48c** (HRMS found m/z 290.2121, compared to calculated m/z 290.2120).



45c **48c** 99%

Scheme 14: Synthesis of Boc-protected benzylpiperidine **48c** via hydrogenation under standard conditions.

The change in shape of the piperidine ring was evidenced by an increased number of signals and complexity observed for the piperidine ring hydrogen atoms in the ^{1}H NMR spectrum, as the ring was less planarised due to the loss of the planar external alkene and therefore adopted a more chair-like conformation resulting in the observed distinct signals for axial and equatorial hydrogens on each carbon atom in the ring. Unlike the alkene **45c** there is free rotation of the substituted benzyl group and therefore the piperidine ring has more symmetry. This is demonstrated clearly in the HSQC spectrum of the product which shows two 2H signals correlating to each carbon signal, indicating distinct axial and equatorial hydrogen environments for chemically equivalent CH_2 groups, and is therefore consistent with expected observations for this structure.

In both the ^{1}H NMR and ^{13}C NMR spectra the piperidine ring signals are still broad due to the presence of the Boc-protecting group, so the magnitude of the J values could not be determined and interpreted. The signals for the CH_2 groups adjacent to the nitrogen atom (H_2 and H_6) are the broadest and show no discernable splitting patterns, but in contrast the H_3 and H_5 signals are further from the Boc-protecting group and some resolution of a splitting pattern can be observed. The equatorial signals are overlapped with the H_4 signal and cannot be directly analysed, but the upfield axial signal shows a clear doublet-of-quartets splitting pattern, which would be expected for the axial hydrogen signals with large coupling constants for geminal coupling and vicinal axial-axial coupling to the H_4 and H_2 signals ($^{2}J_{ax,eq} \approx {}^{3}J_{ax,ax} \approx 12$ Hz), and the smaller coupling to the equatorial H_2 signal ($^{3}J_{ax,eq} \approx 3$ Hz), which

indicates the ring has a more chair-like shape than its precursor **45c**. Further evidence for the change in conformation is demonstrated by comparison of the chemical shifts for the $H_{2/6ax}$ and the $H_{2/6eq}$ signals. The equatorial hydrogen signals appear as a broad signal at 4.06 ppm compared to the axial signals at 2.63 ppm, which is a substantial difference, especially given in the precursor **45c** the different conformation meant there was no difference in chemical shift between two hydrogen atoms attached to the same carbon atom. Some difference is expected for axial and equatorial chemical shifts and equatorial hydrogen signals generally are shifted downfield relative to the axial signals, as observed in the difference between the $H_{3/5ax}$ and the $H_{3/5eq}$ signals which have a shift difference of 0.47 ppm, but a difference of 1.44 ppm is beyond the difference which would be typically expected due to C-C bond anisotropy or sigma-bond donating effects alone. As the Boc-group has partial double bond character and is therefore planarised, the adjacent equatorial hydrogen atoms are in the plane of the π-bonded system and therefore deshielded by anisotropy, resulting in a significant downshield shift of the signal relative to the axial hydrogen signals (Figure 38). If this is the case, the difference between the $H_{2/6ax}$ and the $H_{2/6eq}$ signals would be expected to be significantly less upon removal of the Boc-protecting group to give the desired benzylpiperidine derivative in the subsequent reaction.

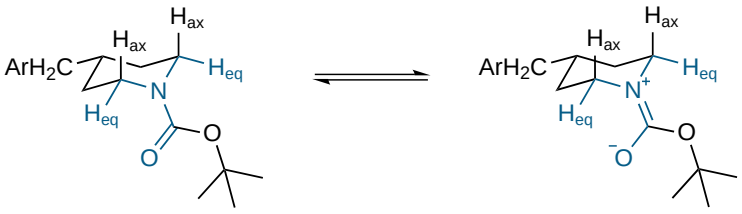
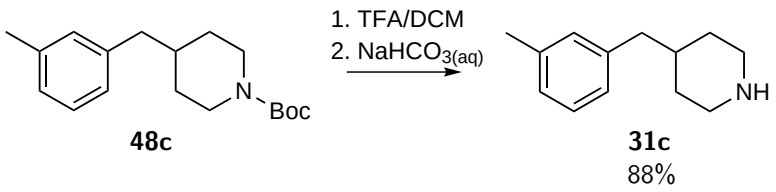


Figure 38: Structure of Boc-protected benzylpiperidine structure showing planarised bond and different chemical environment of axial and equatorial hydrogen atoms.

The final step to yield the desired benzylpiperidine **31c** was removal of the protecting group to give the free amine. The Boc-protecting group is commonly removed under TFA-catalysed conditions in a typically fast reaction. Using this typical method, the compound **48c** was treated with trifluoroacetic acid in dichloromethane, then the acid was neutralised with saturated sodium bicarbonate solution and the amine product **31c** was isolated via extraction (Scheme 15). Due to the water solubility of the amine product, the recovery of the amine was not quantitative despite the fast and complete reaction. A high recovery by liquid-liquid extraction was obtained (88%), showing this was still an effective method for isolation of this derivative.

A fluorine-19 NMR experiment was used to confirm that any residual TFA had been removed from the product sample by evaporation under reduced pressure, and the ^{1}H and ^{13}C NMR spectra showed distinctive changes which confirmed the identity of the product as **31c**. The loss of the large 9H singlet signal in the ^{1}H NMR spectrum for the Boc *tert*-butyl group indicated successful removal of the protecting group, and a broad singlet for the amine



48c **31c** 88%

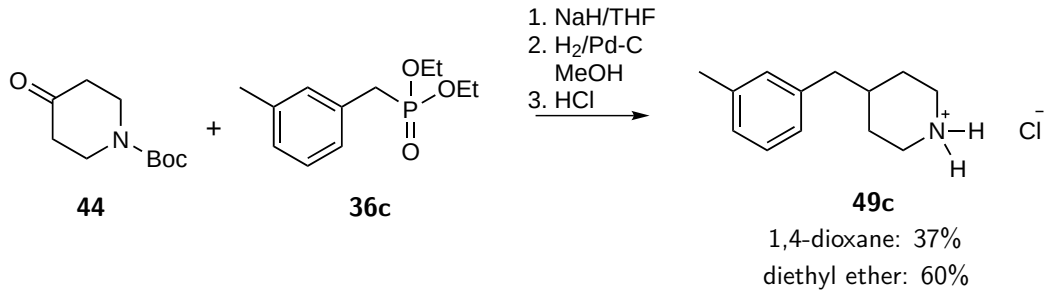
Scheme 15: Synthesis of 3-methylbenzyl extended piperidine derivative **31c** via removal of the Boc-protecting group under acidic conditions.

NH was observed. In contrast to the precursors **45c** and **48c**, the ^{13}C NMR signals of the piperidine ring were not broadened and in the ^{1}H NMR spectrum of the product the characteristic coupling constants corresponding to axial-axial and geminal coupling for a chair-like conformation of the piperidine could be determined. The differences indicate the increased rate of interconversion between conformations of the piperidine on the NMR timescale due to loss of the Boc-protecting group, and clarify the signals to enable analysis of the spectroscopic results. The change in chemical shift of the $H_{2/6eq}$ signal was significant, and the observed upfield shift of this signal to 3.08 ppm (compared to 4.07 for the $H_{2/6eq}$ signal of **48c**) was consistent with the previously postulated hypothesis that the Boc-protecting group was resulting in significantly deshielded equatorial spins for **48c** relative to the $H_{2/6ax}$ signal.

Overall, the yield of **31c** from commercially available starting materials was 77% over 4 steps, with simple purification and isolation of the compounds for each step of the reaction. The high yield and generalisability of the synthetic process to achieve the required range of target benzylpiperidine derivatives was preferable to the alternate literature processes including the reported Grignard synthesis of **31c**, and therefore expected to be the most effective method for synthesis of the remaining required benzylpiperidine derivatives.

An alternate Boc-deprotection method employing a solution of hydrogen chloride in an organic solvent (diethyl ether or 1,4-dioxane) instead of TFA can potentially be used to simplify the isolation of the product. As the reaction with HCl produces the hydrochloride salt of the benzylpiperidine product (**49c**), it would then be anticipated that the product would be a solid and precipitate from the reaction mixture if a relatively non-polar solvent is used, thereby enabling a simpler isolation of the product. The benzylpiperidine hydrochloride is expected to be the only precipitate, and as the synthesis of **45c** and **48c** by Horner-Emmons and hydrogenation reactions respectively were so effective, it was expected that purification of the products at each step would be unneccessary and that collection of precipitated **49c** would be sufficient isolation and would therefore save repeated purification steps (Scheme 16).

This method was attempted using solutions of hydrogen chloride in either diethyl ether or 1,4-dioxane, and in each case the product **49c** precipitated from the solution and was collected by filtration. The reaction in diethyl ether resulted in a higher yield of product compared to the



44 **36c** **49c**

1,4-dioxane: 37%
diethyl ether: 60%

Scheme 16: Synthesis of substituted benzylpiperidine hydrochloride (**49c**) via Horner-Emmons reaction and acid-catalysed Boc-deprotection, with yields from different HCl solution solvents.

deprotection reaction in 1,4-dioxane, indicating that the hydrochloride salt may potentially be partially soluble in 1,4-dioxane which reduced the amount of product isolated by this method. The free amine **31c** was isolated by neutralisation of the hydrochloride salt with aqueous sodium bicarbonate solution and extraction. Good recovery of the product was achieved although, as this required extraction from an aqueous solution, there was some product which was not recovered, similar to the recovery from the TFA-catalysed method. Overall the yield of the desired product **31c** was 41% via isolation of the hydrochloride salt, which was significantly lower than the yield obtained by the stepwise method although it was less labour intensive due to the reduced number of purification steps. Given the recovery of product was still reasonable from this shortened method, it is proposed that either pathway could be used to effectively synthesise a range of benzylpiperidine derivatives.

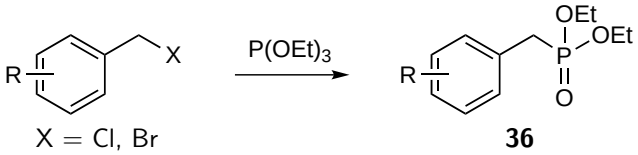
2.3.2 Synthesis of diethyl benzylphosphonate and triphenylphosphonium salt derivatives

The Horner-Emmons approach which was effectively used to synthesise **31c** was then generalised for the attempted syntheses of all remaining derivatives of **31**, as well as the variants **32**, **33**, **34**, and **35**.

The Horner-Emmons reaction pathway requires the diethyl benzylphosphonate derivatives as reagents, and more specifically substituted benzylphosphonates (**36**) were required to synthesise **31**, **32** and **33**, and the diethyl pyridinylmethylphosphonates (**50**) were required for the synthesis of derivatives of **34** and **35**.

The synthesis of a range of mono-substituted diethyl benzylphosphonates had been reported previously and could be achieved readily by reaction of the corresponding benzyl halide with triethylphosphite (Scheme 17).[67,68] In each case the successful reaction was clearly indicated by appearance of a doublet with a large coupling constant (typically $^{2}J_{H,P}$ = 21-22 Hz) in the ^{1}H NMR spectrum corresponding to hydrogen-phosphorous coupling in the product benzylphosphonate. The excess triethylphosphite was distilled from the products which were then used without further purification. The yields of the Michaelis-Arbuzov reactions were

typically high, although reduced yield was observed from some benzyl chlorides which were less reactive than the bromides (Table 4).



Scheme 17: General synthesis of benzylphosphonate derivatives (**36**) via Michaelis-Arbuzov rearrangment.[56]

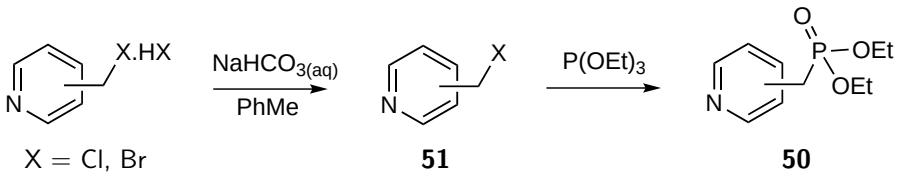
Table 4: Yields of diethyl 4-benzylphosphonate derivatives (**36**) obtained by Michaelis-Arbuzov rearrangement.

	R	X	δ_H PCH_2 (ppm)	$^2J_{H,P}$ (Hz)	Yield 36 (%)
a:	4-^{t}Bu	Br	3.12	21.4	100
b:	2-CH_3	Br	3.17	22.0	100
c:	3-CH_3	Cl	3.11	21.5	100
d:	4-CH_3				[a]
e:	2-OCH_3	Cl	3.25	21.7	88
f:	3-OCH_3	Cl	3.13	21.6	93
g:	4-OCH_3	Cl	3.09	21.2	95
h:	2-F	Cl	3.20	21.6	97
i:	3-F	Br	3.14	21.8	89
j:	4-F	Cl	3.11	21.4	96
k:	2-Br	Br	3.41	22.0	100
l:	3-Br	Br	3.11	21.7	100
m:	4-Br	Br	3.09	21.7	100
n:	2-CF_3	Cl	3.37	22.7	89
o:	3-CF_3	Cl	3.20	21.8	94
p:	4-CF_3	Cl	3.20	22.0	99
r:	3-CN	Br	3.17	21.9	100
s:	4-CN	Cl	3.20	22.3	91
x:	H	Br	3.15	21.6	100

[a] **36d** was synthesised as part of a previous project.

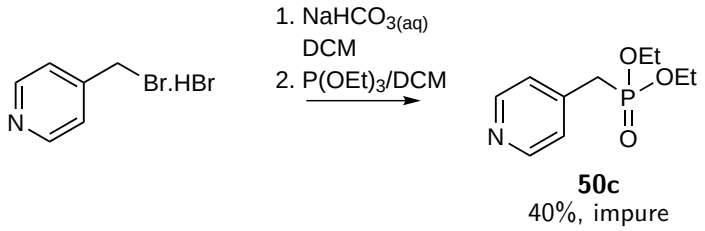
The pyridinyl phosphonate derivatives (**50**) did not have a reported synthesis in the literature, and in this work they proved more difficult to synthesise under the same Michaelis-Arbuzov reaction conditions used for the benzylphosphonates. Initially it was anticipated that the commercially available pyridinylmethylhalide hydrochloride or hydrobromide salts could be treated with aqueous sodium bicarbonate solution to give the pyridine compound **51** which

could be extracted into a volatile solvent, such as dichloromethane or toluene, and then isolated by evaporation of the solvent before the Michaelis-Arbuzov rearrangment under the same conditions used to yield the benzylphosphonate derivatives (Scheme 18).



Scheme 18: Proposed synthesis of pyridinylmethylphosphonate derivatives (**50**) via Michaelis-Arbuzov rearrangment.

The process was complicated by the volatility of the pyridinylmethylhalides (**51**) which meant the starting materials could not be isolated after treatment with the sodium bicarbonate solution required to remove the hydrohalide prior to reaction at reflux in triethylphosphite. This method was attempted in the synthesis of **50c** from 4-(bromomethyl)pyridine hydrobromide but resulted in a pink residue that was found to contain none of the desired product **50c** or the starting material **51c**. Instead, a modified procedure was attempted which involved treatment with the bicarbonate solution and extraction of **51c** into a solvent (toluene or dichloromethane) which was not removed but heated at reflux with triethylphosphite (Scheme 19).

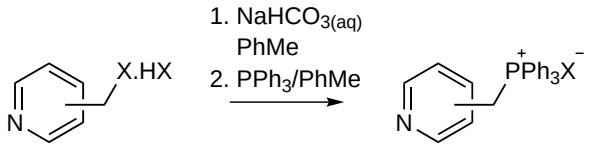


Scheme 19: Attempted synthesis of a pyridinyl-extended phosphonate derivative (**50c**) via a Michaelis-Arbuzov rearrangement.

The reaction in toluene resulted in a crude black mixture which was again found by ^{1}H NMR analysis to contain neither **51c** nor **50c**, and it was suspected that **51c** may have evaporated at the reaction temperature faster than the reaction could occur. The reaction in dichloromethane was at a lower temperature, and gave a small amount of **50c** in a crude mixture. The product was somewhat purified by filtration to remove insoluble impurities and distillation to remove the triethylphosphite, and the resulting brown crude residue was used without complete purification. While not isolated, the signals corresponding to the desired product were evident in the ^{1}H NMR spectrum of the partially purified mixture, and in particular the HP doublet signal ($\delta_H \approx 3.1$ ppm and $^2J_{H,P} = 22.3$ Hz) which was a distinctive observation from the benzylpiperidines above, was clearly evident in the ^{1}H NMR spectrum.

Due to the issues encountered when attempting to make the pyridinyl-analogues of the diethyl phosphonates, alternative methods which avoid the problematic Michaelis-Arbuzov reaction

step were explored. Triphenylphosphonium salts, required for Wittig reactions, are often solids and it was therefore expected that the corresponding pyridinylphosphonium salts (**52**) would be easier to isolate than the phosphonates (**50**) required for Horner-Emmons reactions (Scheme 20). In addition, the reaction to produce Wittig reagents typically proceeds faster than the reaction to make phosphonate derivatives, and it was therefore expected that the formation of **52** derivatives would be higher yielding than the synthesis of **50** as the desired reaction in toluene could potentially progress faster than the evaporation of the volatile pyridine reagent which was considered a factor in the low yield of **50c**.



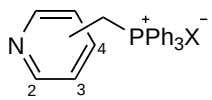
52

Scheme 20: General synthesis of pyridinylmethyltriphenylphosphonium salt derivatives (**52**) in toluene.

The proposed synthesis of the Wittig reagent was used in the attempted synthesis of **52c** from 4-(bromomethyl)pyridine hydrobromide and resulted in a significantly improved yield of **52c**. The product was a solid which could be isolated by filtration, in contrast to the difficult and unsuccessful attempts to isolate the phosphonate **50c**. The expected HP doublet was evident in the ^{1}H NMR spectrum of the product ($\delta_{H} \approx 5.9$ ppm, $^{2}J_{H,P} = 15.9$ Hz), with the distinctive 2-signal splitting pattern for a *p*-substituted ring observed in the aromatic region of the spectrum, as well as large signals corresponding to the phenyl groups.

The other required derivatives (**52a** and **52b**) were also successfully synthesised by this method, with the ^{1}H NMR spectra also consistent with the expected products and an evident HP doublet signal (Table 5). The yield obtained for **52a** was very high, however the yield of **52b** was significantly lower as the chloride reagent was used and therefore the reaction was expected to be slower, giving more opportunity for evaporation of the pyridinyl reagent, **51b**.

Table 5: Results from synthesis of triphenylphosphonium salts (**52**).



52

	Substituent position	X	Yield (%)	δ_H PCH$_2$ (ppm)	$^{2}J_{H,P}$ (Hz)
52a:	2	Br	85	5.63	14.4
52b:	3	Cl	34	5.83	14.9
52c:	4	Br	75	5.86	15.9

From this, the simpler and higher yielding synthesis of the Wittig reagent likely means the Wittig pathway is more feasible for the synthesis of the pyridinylmethylpiperidine (**53**) derivatives, although this is dependent upon the relative reactivity of the reagents in the subsequent Horner-Emmons and Wittig reactions.

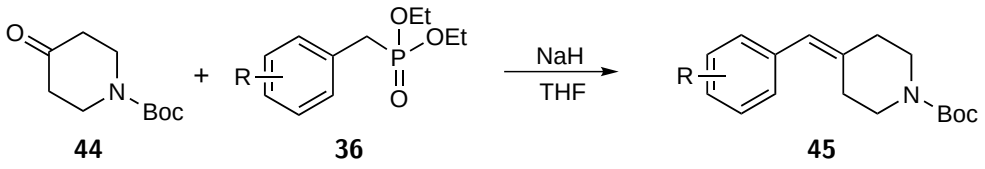
2.3.3 Synthesis of benzylpiperidine derivatives

From the results of the synthesis of **31c**, the proposed method to synthesise the remaining benzylpiperidine derivatives was via a Horner-Emmons reaction with a Boc-protected piperidone or pyrrolidinone, followed by palladium-catalysed hydrogenation of the double bond and TFA-catalysed removal of the Boc protecting group. Although this had not previously been utilised in literature syntheses of the similar 3-benzylpiperidine (**32**) or 3-benzylpyrrolidine (**33**) derivatives it was expected that the same method could be utilised as the same diethyl benzylphosphonate derivatives were required and the Boc-protected reagents **39** and **54** were commercially available.

Given the poor results from attempted synthesis of the analogous pyridine-substituted phosphonate **50c**, the use of a Horner-Emmons reaction in the synthesis of **34** and **35** did not appear to be as viable, and therefore the use of the Wittig reaction would also be explored given the synthesis of the required Wittig reagents **52** had been achieved.

Synthesis of 4-benzylidenepiperidine derivatives via a Horner-Emmons reaction

The Horner-Emmons reactions of the synthesised phosphonates (**36**) with *N*-Boc-4-piperidone (**44**) were conducted using the same conditions as for **45c** above, generally resulting in moderate to good yields of the desired alkene products (Scheme 21, Table 6). In all cases the reaction proceeded to completion, and the resultant purification by chromatography yielded the desired products.

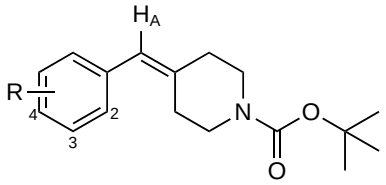


44 **36** **45**

Scheme 21: General synthesis of Boc-protected 4-benzylidenepiperidine derivatives (**45**) via a Horner-Emmons reaction.

Success of the reaction was clearly identified by similar observations in the NMR spectra and HRMS data to that observed for **45c** previously. From the ^{1}H NMR spectra of the products, the presence of an alkene hydrogen signal near 6.3 ppm was distinctive for the desired products (Table 6). Due to the reduced symmetry, four 2H piperidine hydrogen signals were observed for the alkene products instead of the two 4H signals for the piperidone reagent. The piperidine hydrogen signals resembled broad triplets instead of indicating distinct axial and equatorial

Table 6: Yields of Boc-protected 4-benzylidenepiperidine derivatives (**45**) obtained by Horner-Emmons reaction.



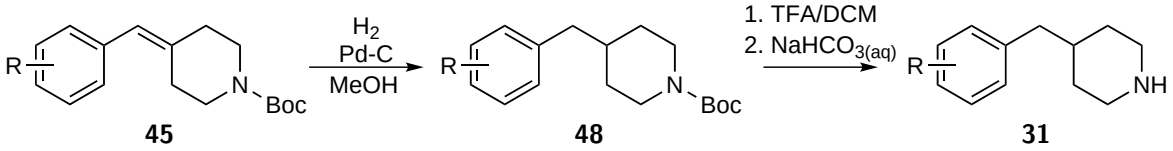
45

	R	δ_H H_A (ppm)	Yield 45 (%)
45a:	4-^{t}Bu	6.32	39
45c:	3-CH_3	6.33	87
45d:	4-CH_3	6.32	51
45e:	2-OCH_3	6.35	56
45g:	4-OCH_3	6.30	27
45i:	3-F	6.32	84
45j:	4-F	6.31	69
45k:	2-Br	6.31	100
45l:	3-Br	6.29	67
45m:	4-Br	6.28	70
45n:	2-CF_3	6.50	82
45o:	3-CF_3	6.37	59
45p:	4-CF_3	6.37	57

hydrogen signals. The lack of separate axial and equatorial hydrogen signals and the broadness of the resultant piperidine signals in both the ^{1}H and ^{13}C NMR spectra again implies that the piperidine ring is substantially planarised and ring-flipping is slow on the NMR timescale for all derivatives synthesised, as the ring structure is constrained by the planar external alkene and the Boc protecting group which has partial double-bond character. Typically, the ^{13}C NMR signals for *N*-adjacent carbon atoms in the piperidine ring were very broad and almost indistinguishable from the baseline of the spectrum, and use of [^{1}H,^{13}C]-HSQC experiments was required to identify the shift of the ^{13}C NMR signals, as was used for **45c** (see Figure 35).

The isolated derivatives of **45** were converted to the Boc-protected 4-benzylpiperidines (**48**) by hydrogenation with palladium on carbon (Pd-C) catalyst under an atmosphere of hydrogen gas in methanol (Scheme 22). The reaction proceeded in quantitative yield to give **48**, and filtration to remove the solid catalyst followed by evaporation of the solvent gave the product typically without the need for further purification.

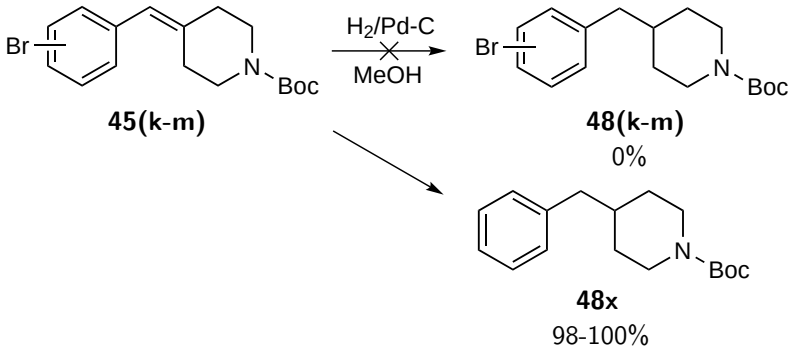
The success of the reaction was clearly evident in the ^{1}H NMR spectra by the loss of the alkene



Scheme 22: General two-step synthesis of 4-benzylpiperidine derivatives (**31**) from benzylidene derivatives (**45**).

signal observed for **45** derivatives and the increase in mass observed by mass spectrometry (HRMS) corresponding to two hydrogen atoms. A more complicated pattern of piperidine ring hydrogen signals was observed, as the loss of the planar alkene enables faster conversion between the ring conformations on the NMR timescale, and so the axial and equatorial signals have distinct shifts. The presence of the Boc-protecting group broadens the signals, as was observed for the precursor **45** derivatives.

Different results were observed for the derivatives with a bromine substituent. The products **48**(**k-m**) were not isolated from the hydrogenation reaction (Scheme 23, Table 7), and instead the NMR spectra and HRMS showed the same product was produced in each of the three reactions. In all cases the alkene signal was not present and the NMR signals observed were consistent with the Boc-protected piperidine rings similar to the other derivatives: instead of the asymmetric piperidine signals observed for the starting material, separate signals corresponding to axial- and equatorial-like hydrogen atoms were observed, with DEPT-edited HSQC experiments showing two inequivalent hydrogen atoms attached to carbon atoms in the piperidine ring, indicating that hydrogenation of the alkene had successfully occurred.



Scheme 23: Attempted syntheses of 4-benzylpiperidine derivatives with bromine substituent **48(k-m)**, giving instead the un-substituted product Boc-protected 4-benzylpiperidine (**48x**).

Table 7: Results of attempted hydrogenations of bromobenzylidene-extended piperidines (**48**) under standard conditions.

Reagent	Br position	Yield 48 (%)	Yield 48x (%)
45k:	2	0	98
45l:	3	0	98
45m:	4	0	100

In contrast to the expected product, however, the aromatic region of the ^{1}H NMR spectrum had higher integration consistent with one additional hydrogen atom, and the splitting pattern of the signals was consistent with a mono-substituted benzene ring instead of the target products (Figure 39). HRMS analysis of the obtained product gave a mass peak consistent with the formula $C_{17}H_{25}NO_2$ instead of the two isotope masses required for the bromo-substituted product, which with the ^{1}H NMR data demonstrates that **48x** was the product obtained from the reaction. The synthesis of **48x** has previously been reported in the literature,[69] and the spectroscopic data for the isolated hydrogenation product from the alkenes **45(k-m)** was consistent with the reported data for **48x**. In this project, each attempted synthesis of **48(k-m)** gave a high or quantitative yield of **48x**, indicating complete hydrogenolysis of the bromide under the hydrogenation conditions (Table 7).

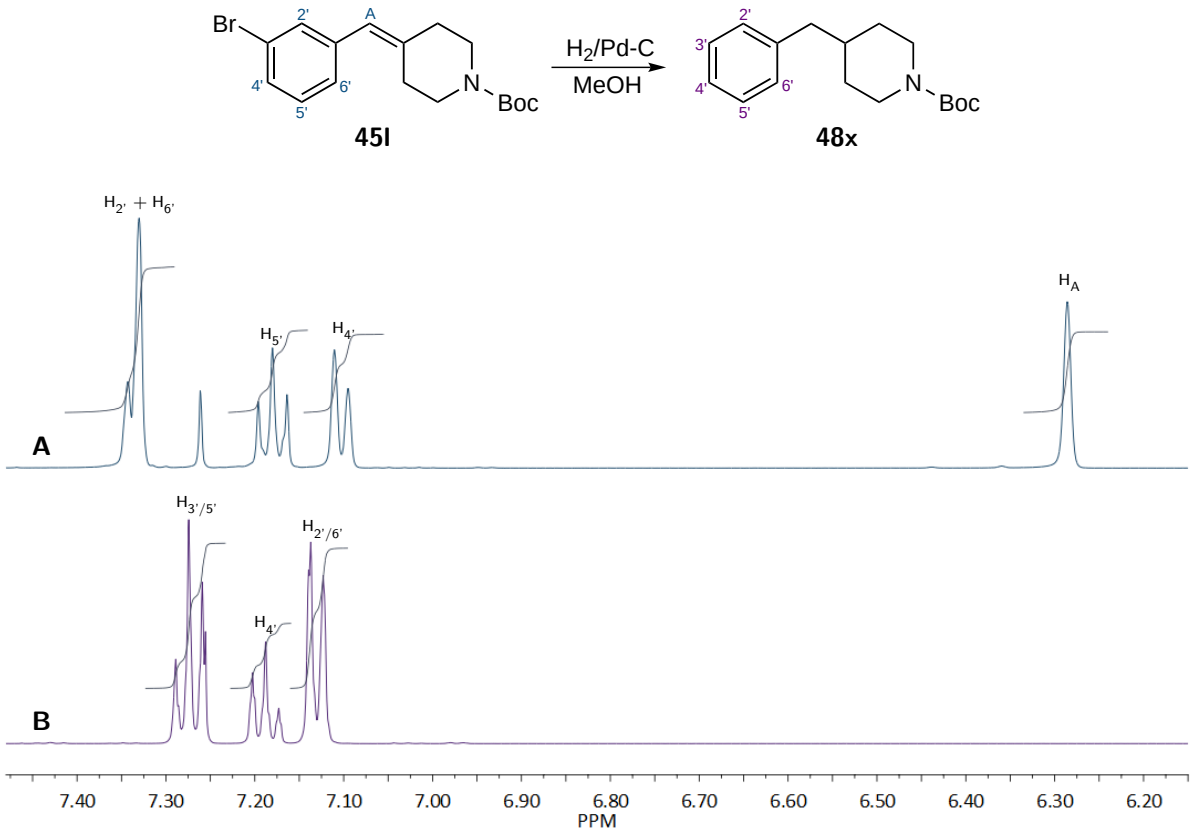


Figure 39: Example ^{1}H NMR spectra demonstrating loss of aryl bromide under hydrogenation conditions. A: Horner-Emmons product with 3'-position bromide substituent **45l**, and B: product from hydrogenation of **45l**, Boc-protected 4-benzylpiperidine **48x**.

Given the hydrogenation resulted in the loss of the aryl bromide bond, the synthesis of the target piperidines **31**(**k-m**) and therefore the target quinoline compound **19**(**k-m**) could not be obtained. The aryl bromides **19**(**k-m**) were not primarily intended to be key target ligand compounds, and instead were intended as intermediates to make more complex extended ligands (see Chapter 3), and these results demonstrate that the proposed synthesis of more complex derivatives must occur via a different intermediate which does not require hydrogenation of an aryl bromide compound.

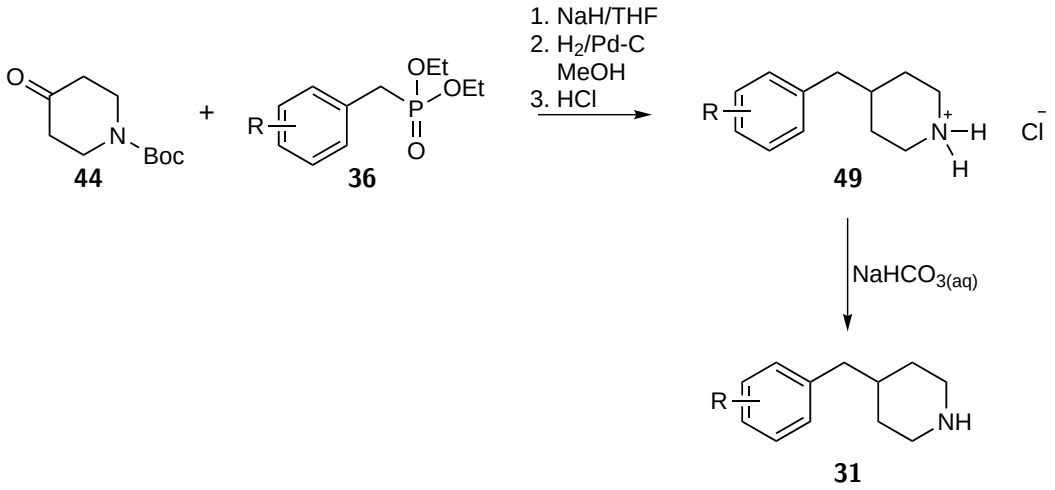
In the cases where the desired derivative of **48** could be obtained, the Boc-protecting group was removed by treatment with TFA in dichloromethane to give the free amine products **31** (Scheme 22, Table 8). The yield from the deprotection reactions varied: some product amines were likely to be more water-soluble and therefore yield was likely lost in the reaction work-up procedure. The removal of the Boc-protecting group simplified the NMR spectra of the products significantly: the line broadening as a result of restricted rotation of the Boc protecting group was no longer evident and therefore was not preventing identification of signals and coupling constants for hydrogen atoms in the piperidine ring: geminal axial-axial coupling and vicinal axial-axial coupling constants (typically 12 Hz) were observed, as well as the smaller vicinal axial-equatorial coupling constants (generally 2-4 Hz). The loss of the large *t*-butyl signals (distinctive 9H singlet at approximately 1.45 ppm in the ^{1}H NMR spectrum, and 28 ppm and 80 ppm in the ^{13}C NMR spectrum) was also observed.

Table 8: Results of sequential reactions of Boc-protected 4-benzylidenepiperidine derivatives (**45**), to give derivatives of **48** and the desired 4-benzylpiperidines **31**.

	Hydrogenation			**Boc-deprotection**		
R		**δ_H H$_{(2/6)eq}$ (ppm)**	**Yield (%)**		**δ_H H$_{(2/6)eq}$ (ppm)**	**Yield (%)**
4-^{t}Bu	**48a:**	4.07	99	**31a:**	3.04	100
3-CH_3	**48c:**	4.06	99	**31c:**	3.27	88
4-CH_3	**48d:**	4.06	100	**31d:**	3.16	100
2-OCH_3	**48e:**	4.04	100	**31e:**	3.04	100
4-OCH_3	**48g:**	4.09	100	**31g:**	3.34	100
3-F	**48i:**	4.08	100	**31i:**	3.35	94
4-F	**48j:**	4.07	100	**31j:**	3.06	94
2-CF_3	**48n:**	4.08	100	**31n:**	3.35	100
3-CF_3	**48o:**	4.08	100	**31o:**	3.30	100
4-CF_3	**48p:**	4.09	92	**31p:**	3.36	96

The alternate method for the synthesis and isolation of **31** derivatives via Horner-Emmons reaction and deprotection with a hydrogen chloride solution (Scheme 24) was attempted for many derivatives in an attempt to obtain the products with less purification steps. The product hydrochloride salts of the 4-benzylpiperidines (**49**) were all solids and precipitated from the hydrogen chloride solution in diethyl ether, which enabled easier isolation of the products but was highly dependent on the quality of the hydrogen chloride solution and also appeared to work poorly for derivatives with more hydrophilic functional groups, and therefore yields varied significantly (Table 9). The hydrogen chloride deprotection conditions resulted in higher yields for some derivatives of **49** compared to TFA deprotection, but the high

variation in the results indicates that the TFA deprotection conditions were more reliable as a general method even though more purification steps were required in the overall synthetic process.



Scheme 24: Synthesis of 4-benzylpiperidine derivatives (**31**) via hydrochloride salt intermediate (**49**).

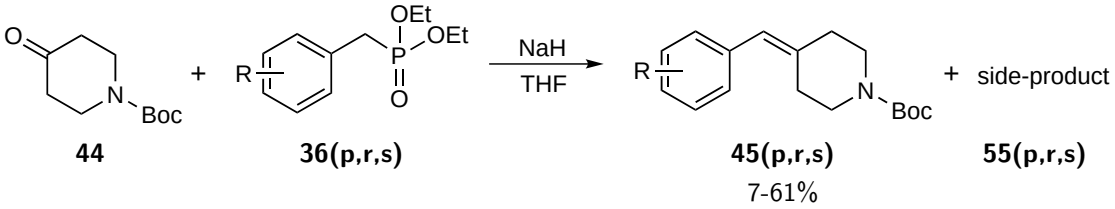
Table 9: Yields of 4-benzylpiperidine hydrochloride derivatives (**49**) from three-step synthesis via a Horner-Emmons reaction (Scheme 24), and recovery of free amine products (**31**).

	R	Deprotection Solvent	Yield 49 (%)	Yield 31 (%)
a:	4-^{t}Bu	diethyl ether	45	79
b:	2-CH_3	diethyl ether	52	70
c:	3-CH_3	diethyl ether	60	69
		1,4-dioxane	37	-
d:	4-CH_3		[a]	41
e:	2-OCH_3	diethyl ether	53	85
f:	3-OCH_3	diethyl ether	59	92
g:	4-OCH_3	diethyl ether	65	77
h:	2-F		[a]	[a]
i:	3-F	diethyl ether	52	68
j:	4-F	diethyl ether	74	74
n:	2-CF_3	diethyl ether	27	-
o:	3-CF_3	diethyl ether	59	-

[a] **49d**, **49h**, and **31h** were synthesised as part of a previous project.

Investigation of Horner-Emmons reaction products

While the Horner-Emmons reaction was generally effective and gave the desired products as reported above, the attempted reactions of *N*-Boc-4-piperidone (**44**) with **36p**, **36r**, or **36s** gave a significant quantity of undesired side-product **55** (Scheme 25). The isolated yield of the desired product was low compared to the other Horner-Emmons reactions despite the complete consumption of the piperidone reagent (Table 10), which with other observations indicated that the undesired product was formed by a competing side-reaction with the limiting reagent. The competing reaction significantly reduced the yield of **45** obtained, and also caused complications in the purification of the desired product. The side-products had a similar R_f value to the desired products and the two products were not entirely separable by column chromatography.



Scheme 25: Attempted Horner-Emmons reaction for synthesis of 4-benzylidenepiperidine derivatives (**45**) where production of a piperidine-type side-product was observed.

Table 10: Results of Horner-Emmons reaction with selected derivatives which give undesired side-product. R_f values given are for TLC with 9:1 hexane/ethyl acetate solvent system.

R		Isolated yield (%)	R_f value		R_f value
4-CF_3	**45p:**	57	0.32	**55p:**	0.30
3-CN	**45r:**	39	0.19	**55r:**	0.18
4-CN	**45s:**	7	0.13	**55s:**	0.10

The difference was most apparent for the attempted synthesis of **45s** where the isolated yield of pure product was only 7%, although a significant amount of impure product co-eluted with the side-product and was also recovered. The amount of the unknown product was considerable: by NMR analysis of the crude reaction mixture or the co-eluted mixture, it was observed that the recovered amount of the side-product **55s** was comparable to the desired product **45s** obtained. The side-product showed similarities to the desired product in the NMR spectra, with signals consistent with a *para*-substituted benzonitrile and a Boc-protecting group, however the side-product also shows distinct differences from the product in the ^{1}H NMR spectrum, with a broad signal at 5.41 ppm instead of the sharper alkene signal at 6.36 ppm observed for **45s**. The presence of signals corresponding to the Boc-protecting group in the spectra of **55s** confirms that the product forms from a competing reaction of the limiting reagent **44**, resulting in the extremely low yield of **45s** recovered compared to other derivatives of **45**.

Although the number of other signals and relative integration of signals were the same as those observed for **45s**, the chemical shifts varied significantly and the signals were broader and had unresolved coupling constants (demonstrated by correlations in the [^{1}H,^{1}H]-COSY NMR experiment). As mentioned previously, broadness in NMR signals is expected if the molecule contains a Boc-protected piperidine group which slows interconversion of the ring conformations on the NMR timescale, however the broadness in the ^{1}H NMR and ^{13}C NMR signals for the side-product was even more enhanced than observed for any derivatives of **45**, and identification by 2D NMR was complicated by the broadness of the signals which both reduced the intensity of any cross-peaks and meant some carbon signals were partially overlapping, therefore making any interpretation unreliable for structure determination. The samples containing the unknown product appeared to be oils, which meant crystallographic methods could not be used for characterisation. Attempted determination of the exact mass found only the mass corresponding to the expected product **45s**.

As identification of the unknown product could not be reliably determined from the data obtained for **55s**, alternative methods of investigating the outcomes of the reaction were explored. As the Boc-protecting group results in broadened NMR signals and hinders analysis of the spectra, and the spectra for indicated **55s** contains a Boc-proecting group, the synthesis of the benzyl-protected analogue **47s** was expected to have more clarified NMR signals and enable use of 2D NMR experiments for characterisation. These expectations were based upon the results observed previously in the synthesis of 3-methylbenzylpiperidine precursor **47c** (see Scheme 13): the desired product **47c** had been obtained in a reasonable yield with no piperidine side-products observed, and NMR experiments showed all ^{13}C NMR signals of **47c** were easily distinguishable and not broadened, and therefore simpler to analyse than the Boc-protected analogue. It was expected that the same change of the protecting group to benzyl would enable better characterisation of the products of the attempted Horner-Emmons reaction with the benzonitrile phosphonate derivative **36s**.

The same Horner-Emmons reaction conditions were used to best replicate the experiment which gave the unknown side-product, although the reaction time for the benzyl-protected piperidone **46** with **36s** was significantly faster than the reaction of *N*-Boc-4-piperidone **44** with **36s**. By ^{1}H NMR analysis of the crude mixture, the reaction appeared to give benzyl-protected product **47s** and a side-product **56s** analogous to the Boc-protected **45s** and **55s** made previously (Figure 40). Aside from the signals corresponding to the protecting groups, the number and shape of the signals in the ^{1}H NMR spectra were the same, although the chemical shifts were different for signals upfield of the aromatic signals which would be expected with a different protecting group. The desired alkene product **47s** had a ^{1}H NMR singlet signal at 6.25 ppm corresponding to the alkene hydrogen (c.f. 6.36 ppm for Boc-protected product **45s**) and four other signals integrating for two hydrogen atoms each for the piperidine ring, similar to the observed spectrum of **45s** (Figure 40A and 40B). Similarly

the side-product had a distinctive broad signal at 5.41 ppm (c.f. broad signal at 5.38 ppm for Boc-protected side-product **55s**) and a series of four upfield broad 2H signals similar to those observed for **55s** (Figure 40C and 40D). From these observations, it was reasonable to suppose that the products were largely analogous, and therefore that characterisation of the benzyl-protected side-product **56s** could lead to better interpretation of the spectra of the Boc-protected product **55s**.

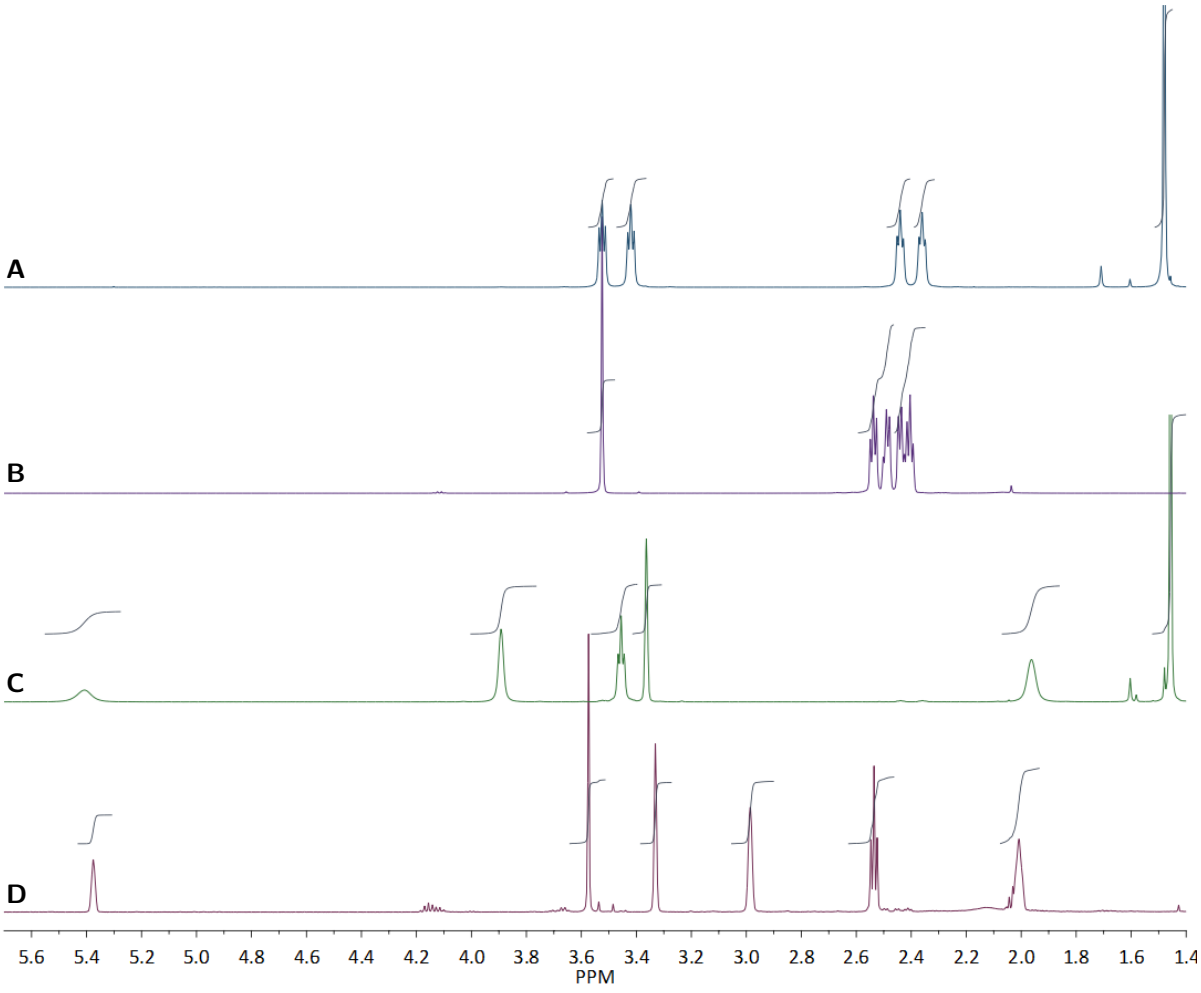


Figure 40: ^{1}H NMR spectrum comparison for benzyl and Boc-protected benzonitrile products (signals upfield of aromatic hydrogen signals shown, δ 5.6-1.4 ppm). A: Boc-protected product **45s**, B: benzyl-protected **47s**, C: Boc-protected side-product **55s**, D: benzyl-protected side-product **56s**. Signals corresponding to atoms in protecting groups are not labelled.

In contrast to the attempted synthesis of the Boc-protected Horner-Emmons reaction product **45s**, the desired benzyl-protected benzylidenepiperidine product **47s** was produced in a significantly higher proportion compared to the unknown side-product **56s**. The reason for this is unclear, but may indicate the rate of formation of unknown product is slower than formation of the Horner-Emmons product, or that the unknown compound is the product of a further reaction from the Horner-Emmons product that occurs given sufficient time, and given the much faster reaction with the benzyl-protected piperidone the side-reaction had less time to progress. The products were still difficult to completely separate by column chromatography

but the unknown benzyl-protected product streaked less which meant pure fractions of each product could be obtained.

The ^{1}H NMR spectrum of the unknown product **56s** still contained many broad signals with unresolved coupling constants, indicating that some structural feature was affecting the bond-rotation or interconversion of conformations of the structure even without the presence of a Boc-protecting group. Despite this, and in contrast to the Boc-protected analogue, it was observed that the ^{13}C NMR signals of the side-product were sharp and did not overlap. The increased clarity of the ^{13}C NMR spectrum enabled more reliable interpretation of 2D NMR experiments to characterise the structure of the unknown side-product.

The [^{1}H,^{13}C]-HMBC data for **56s** was used to confirm that the *para*-benzonitrile structure was indeed present, however signals from the benzonitrile ring showed correlations to a broad signal with a 2H integration in the ^{1}H NMR spectrum. This signal was confirmed to be a methylene CH_2 group by the DEPT-edited HSQC experiment, which indicates that the reaction product is not a cyano-substituted benzylidene: in contrast, a benzylidene product like **47s** would show a correlation to a 1H integration alkene signal. The HSQC experiment also showed that the characteristic side-product 1H signal at 5.38 ppm is attached to a carbon atom with a shift at 122.3 ppm in the ^{13}C NMR spectrum, and therefore the side-product is also likely an alkene (Figure 41A).

Further analysis of the spectroscopic data and the 2D NMR experiments led to postulation of a new structure for the benzyl-protected side product. HRMS analysis of the isolated compounds identified that these are likely structural isomers, as the same mass peak was observed for each product. The DEPT-edited HSQC experiment was used to determine which NMR signals corresponded to methylene groups (Figure 41A), and the HMBC correlations of these signals to other methylene groups and the sp^2 hybridised carbon atoms demonstrated that the data was consistent with a tetrahydropyridine structure instead of a piperidine (Figure 41B).

Following identification and characterisation of the side-product, it could be determined from ^{1}H NMR analysis of the Horner-Emmons reaction mixture that the two isomeric benzyl-protected products were produced in a 9:1 ratio, favouring the desired piperidine product **47s** (Scheme 26).

As the benzyl-protected postulated structure **56s** is a structural isomer of the Horner-Emmons reaction product **47s** with the alkene in an adjacent position, it was therefore expected that the hydrogenation reactions of **47s** and **56s** would yield the same product, **57s** (Scheme 27). Firstly, the hydrogenation of **47s** was conducted under standard conditions to give one major product which was determined to be **57s**. The structure of the product was confirmed by HRMS which showed mass increase corresponding to two hydrogen atoms and the NMR spectroscopic data which was consistent with the expected structure, with loss of the alkene signal and change in appearance of the ^{1}H NMR signals indicative of a chair-like

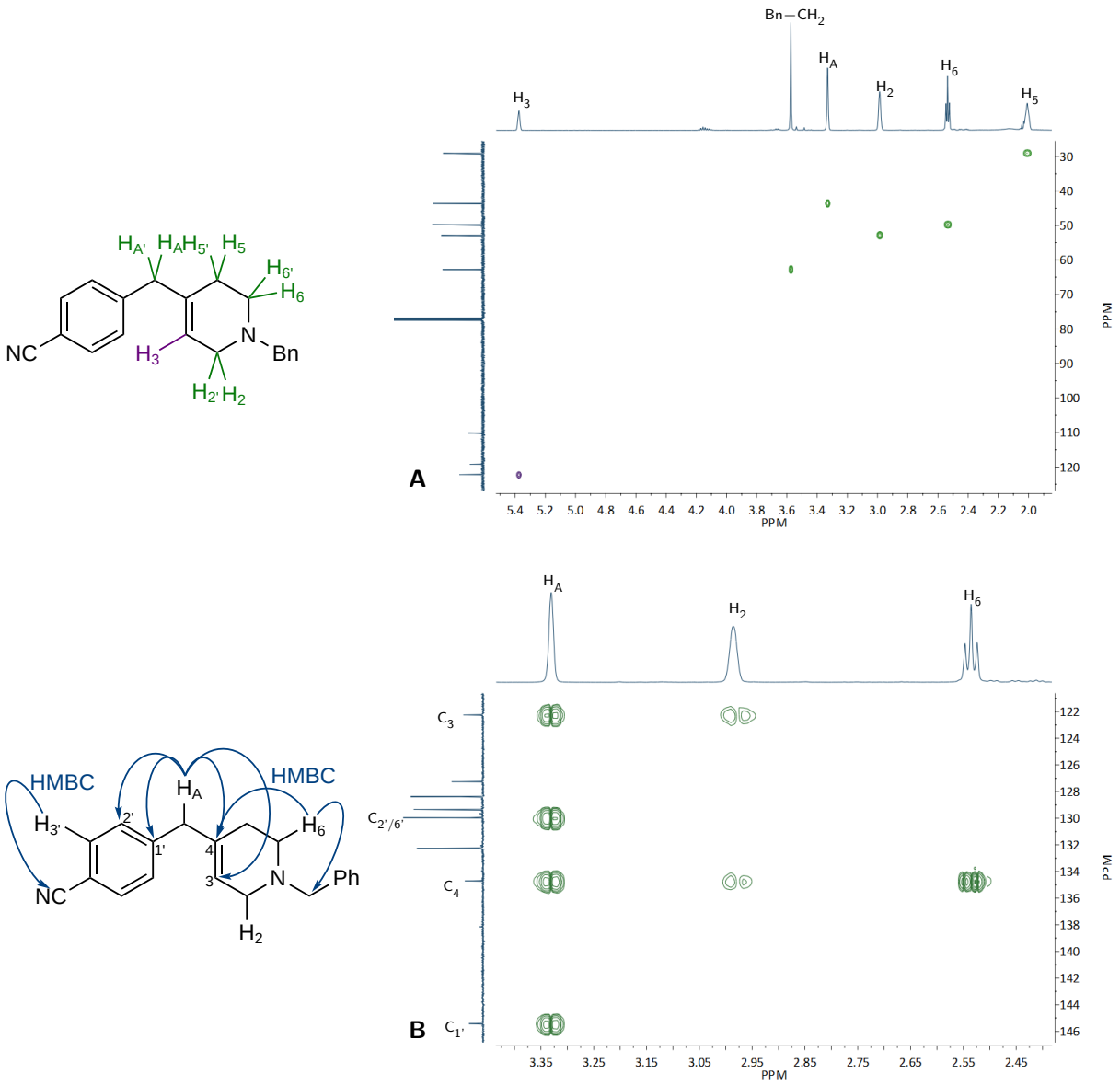
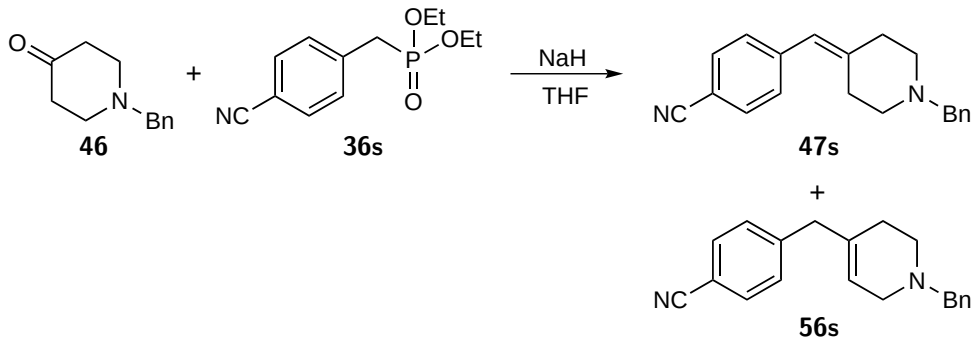
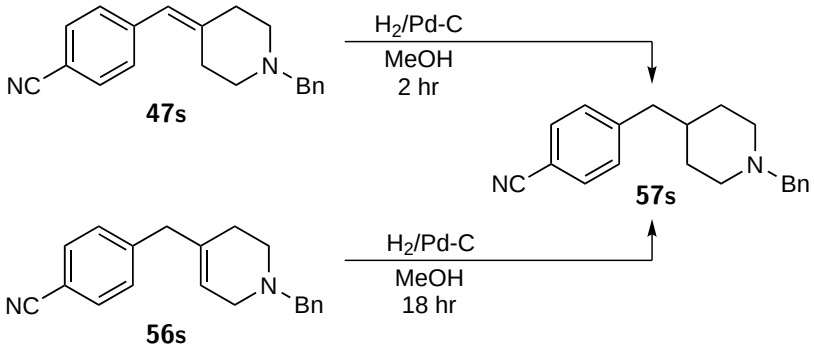


Figure 41: 2D NMR experiments used to determine structure of Horner-Emmons side-product. A: DEPT-edited HSQC for upfield hydrogen signals, and B: HMBC spectrum showing correlations between upfield hydrogen with sp^2 hybridised ^{13}C NMR signals.



Scheme 26: Products of Horner-Emmons reaction with *N*-Bn-4-piperidone (**46**) and diethyl 4-cyanobenzylphosphonate (**36s**). Ratio of products determined from ^1H NMR spectrum was 9:1, favouring **47s**.

piperidine ring and *para*-substituted benzyl group, all consistent with **57s**, and the benzyl-protecting group was still evidently present. While the desired product **57s** was the major product of the reaction, there were traces of other products observed by NMR analysis of the crude reaction mixture. It is expected that these signals are due to further reduction of the CN functional group, but these were only present in small quantities which could not be isolated and characterised. Using the same reaction conditions, the hydrogenation of the Horner-Emmons side-product **56s**, postulated to be the tetrahydropyridine isomer of **47s**, was performed and resulted in one major product with the same spectroscopic results consistent with **57s**, clearly showing the reactions of each Horner-Emmons product proceeded to give the same compound.

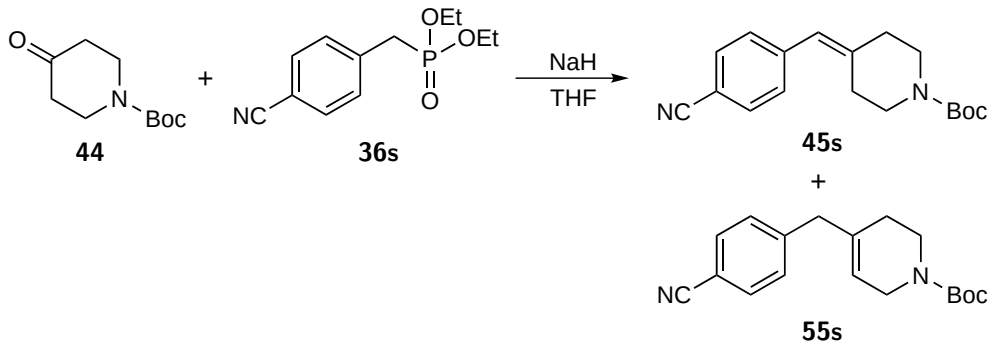


Scheme 27: Hydrogenation of isomeric products (**56s** and **47s**) isolated from Horner-Emmons reaction.

Notably, the hydrogenation reaction of **56s** took a significantly longer time to achieve complete reduction of the alkene bond. The conversion of **47s** to **57s** took 2 hours, which was typical for hydrogenation of the benzylidenepiperidine derivatives, whereas **56s** required a longer reaction time of up to 16 hr for complete reaction. The difference in reaction time therefore indicates significant differences in the 3D conformations of the structure. The slower reaction suggests that the alkene of the tetrahydropyridine ring in **56s** is less sterically accessible than the alkene of the benzylidenepiperidine isomer **47s**, which therefore resulted in a reduction in the rate of palladium catalysed reduction under the same reaction conditions.

Given that the products of the benzyl-protected reaction could be characterised, the observations and spectroscopic results were then compared to the Boc-protected version to determine if the analogous deductions could be made. There were obvious differences between the syntheses of **55s** and **56s**, particularly that with a benzyl-protecting group the side-product **56s** was produced in significantly lower quantities compared to the target benzylidenepiperidine product **47s**. There were also very obvious similarities in the spectroscopic data (see Figure 40). As mentioned previously, the HRMS data for a sample of **55s** showed a mass peak the same as what was observed for **45s**, showing this product could also be a structural isomer of the expected Horner-Emmons product **45s**. While the 2D NMR experiments could not be reliably analysed due to overlap and broadness of signals,

the ^{1}H NMR spectrum and ^{13}C NMR spectrum of **55s** showed broad similarity to the spectra of the benzyl analogue **56s**. In particular, with the exception of signals for the protecting groups, the number of signals and relative integrations of signals for each product were the same and appeared very similar. The ^{1}H NMR signals for the methylene groups adjacent to the protected nitrogen atoms were shifted significantly further downfield relative to the signals for **56s**, however this is expected due to the change in protecting group. Overall, the consistencies in spectroscopic data observed strongly support that the side-product of the reaction with Boc-protected **44** and **36s** is the tetrahydropyridine compound **55s** - the analogous Boc-protected structure to benzyl-protected **56s** (Scheme 28).



Scheme 28: Deduced products of Horner-Emmons reaction with *N*-Boc-4-piperidone (**44**) and diethyl 4-cyanobenzylphosphonate (**36s**). Ratio of products determined from ^{1}H NMR spectrum was 2:7, favouring **55s**.

The tetrahydropiperidine compound **55s** had not been reported in the literature previously. Interestingly, the reaction of **36s** and the piperidone **44** had been reported in patents previously, although there was no reference to the structure **55s** or any indication of any side-reaction reported in either instance.[62,70] Similar syntheses of tetrahydropyridine compounds had also not been previously reported. Tetrahydropyridines are interesting structures in organic synthesis and various derivatives have been promising targets in drug development research, but they are not widely reported due to the difficulties in selectively preparing and isolating this particular structure.[71,72] Commonly, tetrahydropyridines are synthesised via selective hydrogenation of a pyridine ring, and while complex reagents and methodologies have been studied in order to improve the selectivity and avoid complete reduction to the saturated piperidine ring, only a limited scope of extended tetrahydropyridines structures have been effectively prepared.[73,74] In comparison, the Horner-Emmons reaction conditions which yielded the tetrahydropyridine product **55s** are very mild and the reaction was comparatively fast, and the tetrahydropyridine was the major product of the reaction. High pressures and expensive catalysts were not used, and therefore if conditions could be obtained which optimise formation of the tetrahydropyridine (such as **55s**), over the benzylidenepiperidine product (**45s**) then this approach would be a substantially improved method upon reported synthetic processes.

The mechanism of synthesis for the side-product **55s** was still unclear. The side-product was

never the only product, and some of the desired product **45s** was always present, therefore it was considered that the side-product **55s** may be a product of a further reaction after **45s** had formed by the Horner-Emmons reaction mechanism under the reaction conditions. To test this, a pure sample of **45s** (^{1}H NMR spectrum shown in Figure 42A) was treated with sodium hydride in THF for 16 hours, and resulted in a mixture of both **45s** and **55s** (Figure 42B), showing that **55s** can be produced from **45s** under the Horner-Emmons reaction conditions in the absence of any further piperidone or phosphonate reagents. The same experiment was attempted using a pure sample of **55s** (Figure 42C) treated with the same conditions, which also yielded a mixture of both structural isomers (Figure 42D).

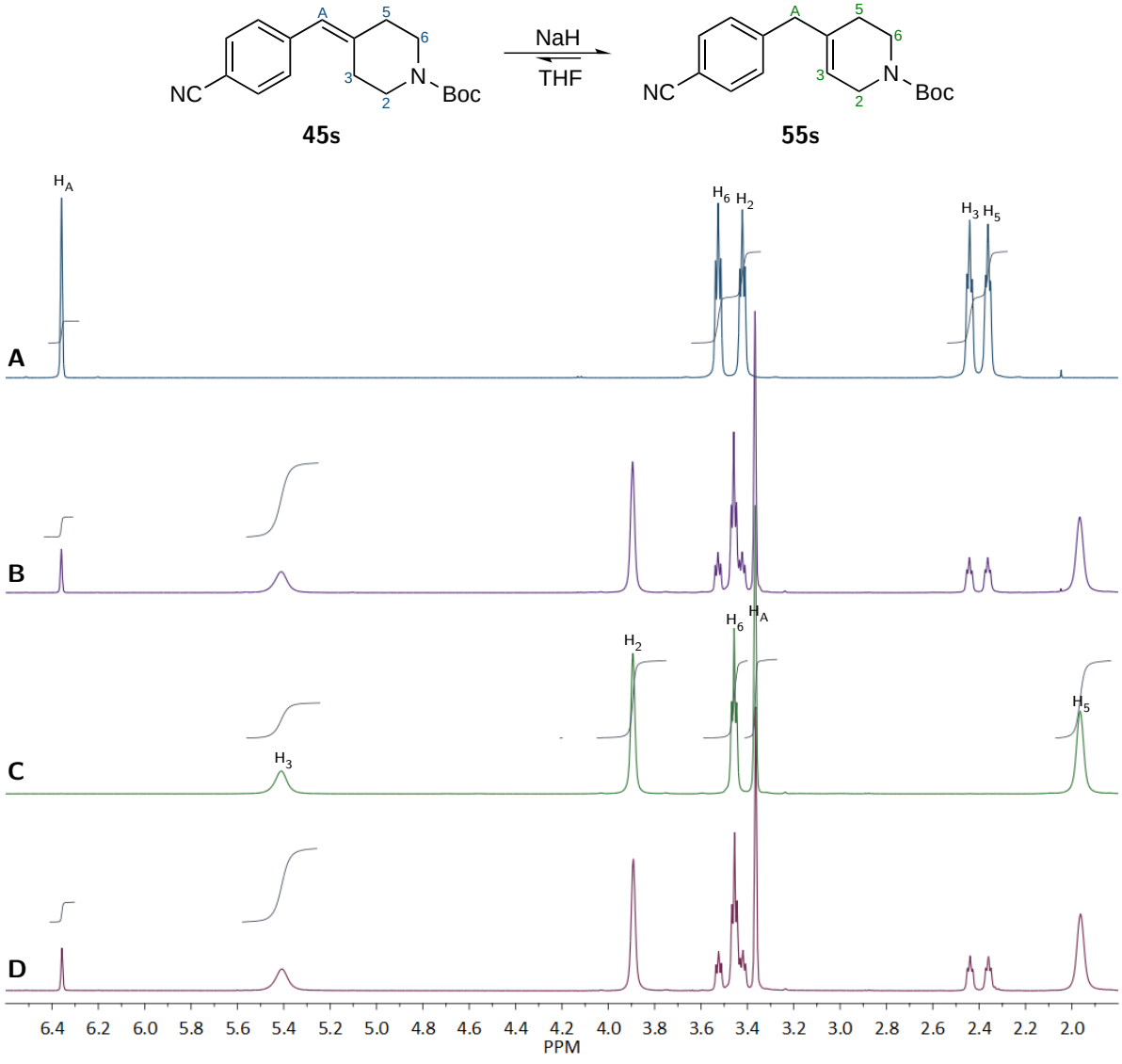


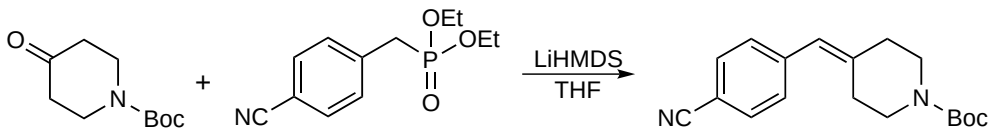
Figure 42: Comparison of ^{1}H NMR spectra (δ_H 1.8 - 6.6 ppm) demonstrating isomerisation of benzonitrile-extended Horner-Emmons reaction products (**45s** and **55s**) upon treatment with sodium hydride in THF. A: Pure sample of expected Horner-Emmons product **45s**, B: mixture after treating **45s** with sodium hydride in THF for 16 hr, C: pure sample of Horner-Emmons side-product **55s**, and D: mixture after treating **55s** with sodium hydride in THF for 16 hr. In each case, the ratio of products was approximately 7:2, favouring the side-product **55s**.

The experiments showed the two structural isomers are able to interconvert under Horner-

Emmons reaction conditions, and interestingly the ratio of the two isomers was the same in each resultant reaction mixture, both times favouring formation of the tetrahydropyridine isomer **55s** over the expected Horner-Emmons reaction product (Figure 42). No reaction intermediates or other products were observed and there was complete mass recovery from the reactions. Similar tests without addition of the base, NaH, showed no isomerisation, indicating the reaction is base-catalysed.

The interconversion of the isomers appears to be dependent upon the benzyl substituent: as reported above, most derivatives were successfully synthesised with reasonable yields and there were no observations of the side-product **55**. For only a few derivatives was the presence of the tetrahydropyridine side-product observed, and all of these derivatives contained an electron-withdrawing benzyl substituent. For these derivatives, the relative quantities of the side-product varied significantly, and some derivatives favour the production of the side-product over the desired product. While no experiment so far has indicated the presence of any reaction intermediates, the need for an electron-withdrawing functional group could indicate that the isomerisation proceeds through a charged intermediate which is stabilised by the ability to delocalise electrons into the electron-poor benzene ring. In this process, it was speculated that the sodium hydride base could be facilitating the isomerisation reaction, or that the degradation of the base over time may result in some sodium hydroxide being present in the reaction mixture, which could potentially result in an unanticipated reversible side-reaction.

To test the effect of the base on the resultant product mixture, LiHMDS was used in the Horner-Emmons reaction to make **45s** from Boc-protected piperidone **44** and phosphonate **36s**, keeping all other conditions the same (Scheme 29). In this experiment the product **55s** was not detected at all, and a high yield (91%) of pure **45s** was isolated. This experiment supports the theory that the synthesis of **55s** is base dependent and may involve reaction with sodium hydride (or sodium hydroxide), although further investigation is required to definitively determine the mechanism.

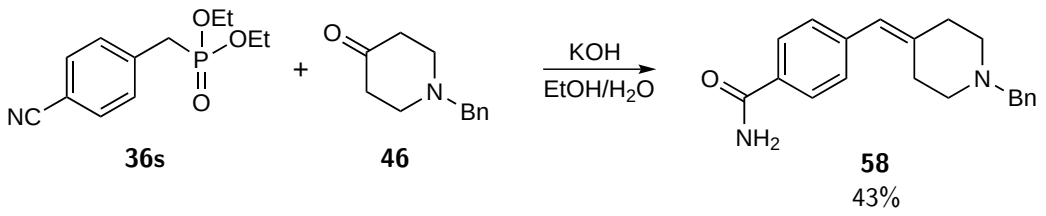


44 **36s** **45s** 91%

Scheme 29: Horner-Emmons reaction of diethyl 4-cyanobenzylphosphonate (**36s**) with Boc-protected piperidone **44**, using LiHMDS used as the base.

Although these results indicate that the synthesis of both structural isomers **45** and **55** may be expected with hydride or hydroxide bases under Horner-Emmons reaction conditions when the benzyl substituent is an electron-withdrawing group, a similar synthesis reported in a patent suggested that the Horner-Emmons reaction with **36s** and a *N*-protected piperidone

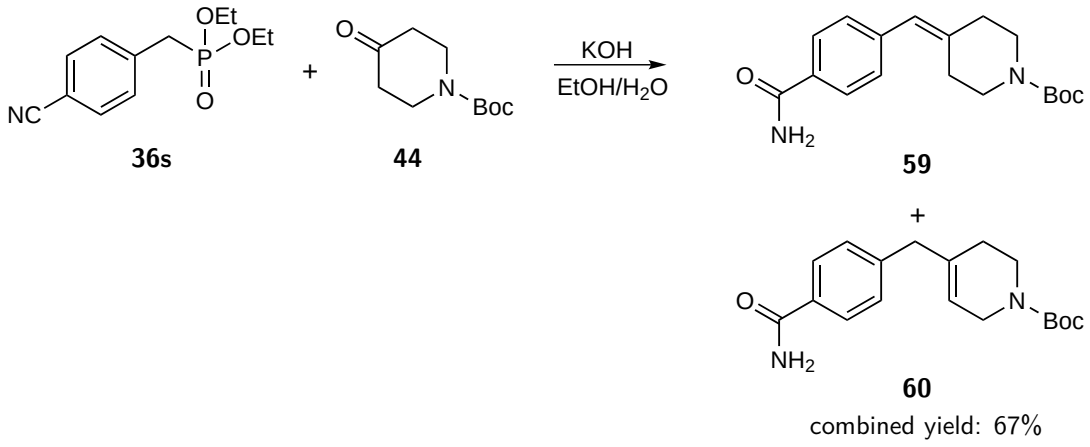
can occur using potassium hydroxide as the base in ethanol with water (Scheme 30.)[75]



36s **46** **58** 43%

Scheme 30: Published Horner-Emmons reaction of diethyl 4-cyanobenzylphosphonate (**36s**) with benzyl-protected piperidone **46**, using potassium hydroxide as the base.[75]

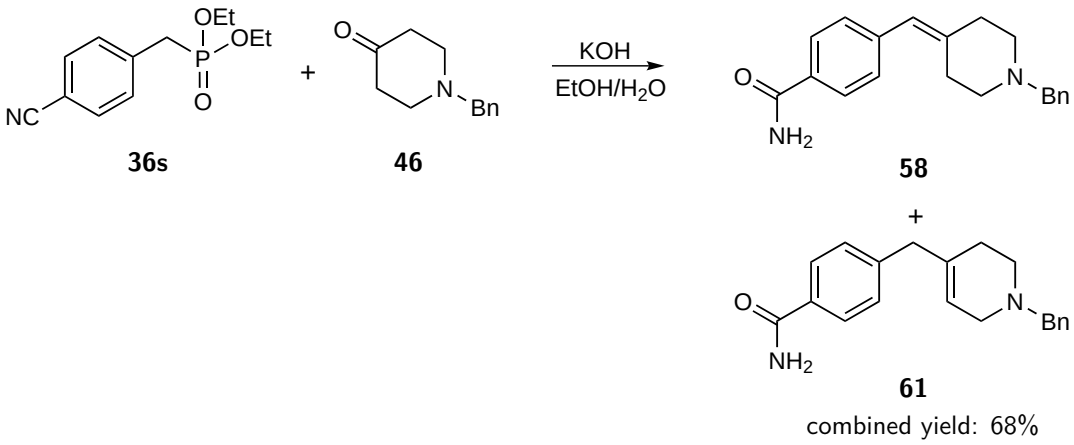
In the reported literature synthesis, the hydrolysis of the benzonitrile to a benzamide also occurs to give the product **58**. Both nitrile and amide benzyl substituents are electron-withdrawing by resonance, and the previous results of this project have indicated that electron-withdrawing functional groups facilitate the unexpected isomerisation to give the tetrahydropyridine products. The reported method had no mention of side-product formation, which would indicate that sodium hydride, instead of any hydroxide present, is the base enabling the isomerisation under the Horner-Emmons reaction conditions in the attempted syntheses of this project. The use of hydroxide as the base for a Horner-Emmons reaction is not common as it is not typically a strong enough base to deprotonate the phosphonate and might instead be expected to hydrolyse the phosphonate (see Scheme 11). To test the efficacy of the literature method, the reaction of **36s** with *N*-Boc-4-piperidone (**44**) was attempted under the published condtions to determine if only the benzamide product **59** would be obtained (Scheme 31), and the reaction with *N*-Bn-4-piperidone (**46**) as reported in the patent was also attempted, expecting to yield the stated product **58** (Scheme 32, cf. Scheme 30[75]).



36s **44** **59** + **60** combined yield: 67%

Scheme 31: Products of Horner-Emmons hydrolysis reaction with *N*-Boc-4-piperidone (**44**) and diethyl 4-cyanobenzylphosphonate (**36s**). The ratio of products **59** and **60** was approximately 3:4, as determined by ^{1}H NMR analysis of the mixture.

In both cases the presence of significant amounts of the tetrahydropyridine isomer product was observed (**60** or **61** respectively). The side-product was synthesised in greater quantities



36s **46** **58** + **61**

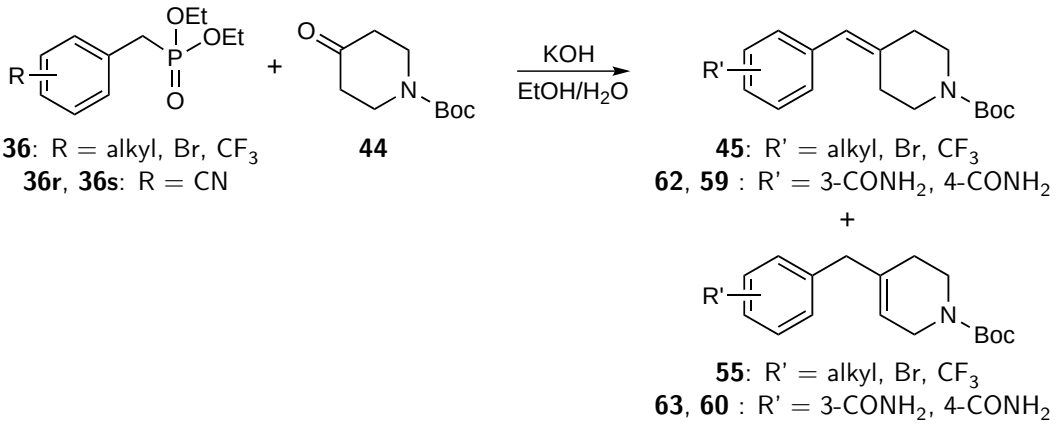
combined yield: 68%

Scheme 32: Products of Horner-Emmons hydrolysis reaction with *N*-Bn-4-piperidone (**46**) and diethyl 4-cyanobenzylphosphonate (**36s**), following the literature method reported previously (see Scheme 30).[75] The ratio of products **58** and **61** was approximately 9:1, as determined by ^{1}H NMR analysis of the mixture.

than the desired product for the Boc-protected piperidine (3:4 ratio by ^{1}H NMR analysis, not separable), although in the Bn-protected analogue the side-product **61** was produced in significantly lower quantities (<10% by ^{1}H NMR analysis, not separable from mixture). The results obtained for these experiments, and the consistency with the previous Horner-Emmons reaction attempts (Table 10), indicated that the published method was likely to have also produced the tetrahydropyridine isomer (**61**) even though this was not reported, and therefore the use of potassium hydroxide as the base was not useful to resolve the issue of isomerisation.

While this supported the initial hypothesis that the isomerisation is dependent on the presence of hydroxide base, it also demonstrated that potassium hydroxide was an effective base for Horner-Emmons synthesis of the isomeric mixture only when the phosphonate had electron-withdrawing benzyl substituents (Scheme 33, Table 11). No reaction was observed with other derivatives when potassium hydroxide was the only base used. It is possible that the ability to delocalise charge into the electron-poor benzyl group stabilises a reaction intermediate to enable the Horner-Emmons reaction to proceed, therefore a weaker base such as hydroxide can be used. While stability of the reaction intermediate appears to be a key factor in enabling the reaction, there is not sufficient evidence to conclude that the formation of the two isomeric products proceeds via a Horner-Emmons reaction mechanism, and it is possible that both isomers are formed by an alternate pathway.

The hydrogenation of the benzonitrile isomers **45s** and **55s** gave predominantly the desired product **48s** but there were still some undesired minor side-products, likely due to further reduction of the nitrile bond. The benzonitrile target compounds were the only compounds containing a benzyl susbtituent which was electron withdrawing by resonance and increased the lipophilicity of the final target ligand compounds, however given the synthesis of **59** and **60** by Horner-Emmons and hydrolysis reactions had been achieved it was determined that



36: R = alkyl, Br, CF_3
36r, **36s**: R = CN

44

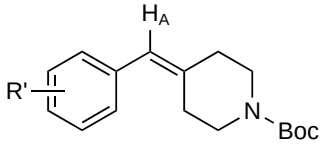
45: R' = alkyl, Br, CF_3
62, **59** : R' = 3-$CONH_2$, 4-$CONH_2$

+

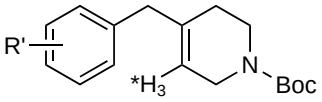
55: R' = alkyl, Br, CF_3
63, **60** : R' = 3-$CONH_2$, 4-$CONH_2$

Scheme 33: Attempted Horner-Emmons hydrolysis reactions of benzylphosphonates (**36**) and *N*-Boc-4-piperidone (**36**) with potassium hydroxide.

Table 11: Results of attempted Horner-Emmons hydrolysis reactions of benzylphosphonates (**36**) and *N*-Boc-4-piperidone (**36**) with potassium hydroxide.



45,**59**,**62**



55,**60**,**63**

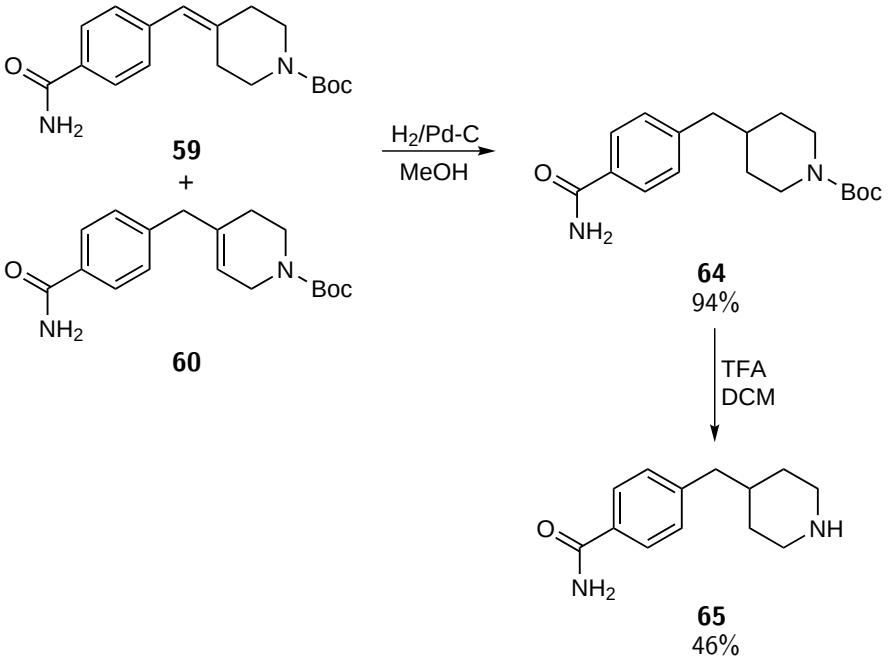
	R' =	Observed products	Product 45: δ_H H_A (ppm)	Side-product 55: δ_H *H_3 (ppm)	Approx. ratio 45:55
a:	4-^{t}Bu	none	-	-	-
c:	3-CH_3	none	-	-	-
l:	3-Br	**45l**, **55l**	6.29	5.39	5:1
n:	2-CF_3	**45n**, **55n**	6.50	5.28	49:1
p:	4-CF_3	**45p**, **55p**	6.38	5.41	1:3

R' =	Observed products	Product δ_H H_A (ppm)	Side-product δ_H *H_3 (ppm)	Approx. product ratio
3-$CONH_2$	**62**, **63**	6.38	5.39	7:1
4-$CONH_2$	**59**, **60**	6.38	5.40	3:4

benzamide derivatives were likely to be preferable synthetic targets to the benzonitriles. The amide group is also electron-withdrawing by resonance and hydrophilic, and the synthesis is simplified despite the isomerisation to two alkenes in the hydrolysis reaction as both alkene isomers can be reduced to give the benzylpiperidine **64** by hydrogenation without any further reduction of the functional group. The nitrile group is also reactive and less likely to be an useful functional group in a final ligand compound due to reactivity in biologically-relevant

conditions, even though it is an interesting structure to investigate the binding affinity with the target protein. The amide is more stable, although it is likely to hydrolyse to the carboxylic acid under harsher conditions.

Using the standard hydrogenation conditions, a mixture of the two products of the Horner-Emmons reaction (**59** and **60**, 2:7 ratio) was reduced to the Boc-protected piperidine (Scheme 34). A longer hydrogenation reaction time of 16 hr was required to ensure complete reduction of the structurally different alkenes **59** and **60**, as had been observed for the hydrogenation of benzonitrile-substituted tetrahydropyridine compound **56s** previously. Treatment with TFA then removed the Boc-protecting group to give **65**, with spectroscopic analysis used to confirm the expected chair-like confirmation of the piperidine ring as described previously, and demonstrate successful removal of the Boc-protecting group. Despite the mixture of alkenes used in the synthetic procedure and the longer reaction time required for the hydrogenation, the synthesis of the benzamide compound **65** gave results consistent with the other 4-benzylpiperidine derivatives prepared previously.

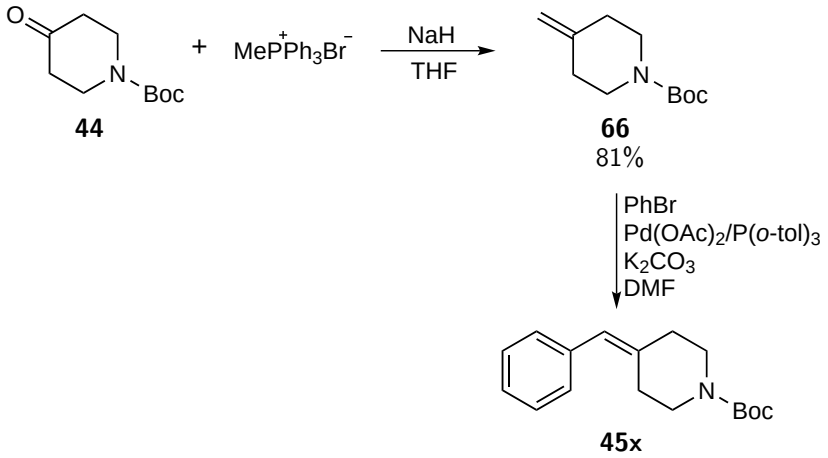


Scheme 34: Synthesis of benzamide-extended piperidine compound **65**, via hydrogenation of a mixture of alkenes **59** and **60**.

Alternate methods for synthesis of 4-benzylpiperidine derivatives

As an alternate method, the Heck reaction pathway was attempted to avoid complications with the phosphonate reactivity and competing reactions observed for the Horner-Emmons reactions. This involved synthesis of *N*-Boc-4-methylidenepiperidine (**66**) using a Wittig reaction, followed by palladium-catalysed coupling with bromobenzene. Wittig reaction conditions were investigated to give **66** from *N*-Boc-4-piperidone and methyltriphenyl-phosphonium bromide in good yield (Scheme 35). A range of reaction conditions were

investigated, and using sodium hydride as the base gave the highest conversion to the desired product. The synthesis of the terminal alkene was evident by NMR analysis of the purified product, with the 2H alkene signal at 4.75 ppm. Other signals were very similar to the piperidone reagent, showing the shape of the structure did not significantly change.



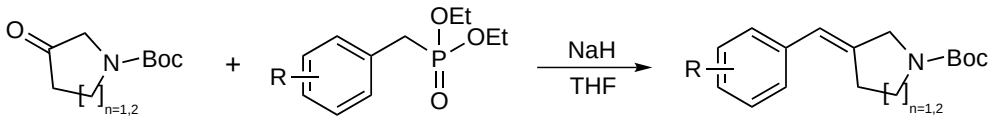
Scheme 35: Attempted synthesis of Boc-protected 4-benzylidenepiperidine (**45x**) via Wittig and Heck reaction pathway.

A range of Heck reaction conditions were attempted on a small scale to test the efficacy of the palladium-catalysed reaction. For most conditions no reaction was observed. A catalyst system of $Pd(OAc)_2$ and tri(*o*-tolyl)phosphine ($P(o\text{—}tol)_3$) appeared to show some successful synthesis of **45x** as a minor component of a complex mixture of products which could not be purified. The poor results of the Heck reactions attempted and the need for an additional carbon-carbon bond forming reaction to make **66** (compared to the very successful synthesis of phosphonate derivatives **36** required for Horner-Emmons reactions) meant the Horner-Emmons reaction pathway was most effective in this work and used to make all derivatives of **31**.

Horner-Emmons synthesis of 3-benzylpiperidine and 3-benzylpyrrolidine derivatives

Due to the success of the Horner-Emmons reactions in the synthesis of the range of 4-benzylidenepiperidine derivatives **45**, this method was also expected to yield the required Boc-protected 3-benzylidinepiperidine and 3-benzylidenepyrrolidine derivatives, **67** and **68** respectively. While this method was not utilised in the literature preparations of the small range of reported derivatives of **32** and **33**, the reported syntheses were typically lower yielding and expected to be more complicated than the Horner-Emmons reactions method which proved to be effective for the syntheses of **45** derivatives in this work. It was therefore expected that the optimised Horner-Emmons reaction conditions used to synthesise the **45** derivatives would yield the corresponding 3-substituted products (Scheme 36) .

The reactivity of the different *N*-Boc protected piperidones **44**, **39**, and **54** was found to



n = 2: **39**
n = 1: **54**

36

n = 2: **67**
n = 1: **68**

Scheme 36: General synthesis of 3-benzylidenepiperidine (**67**) and 3-benzylidenepyrrolidine (**68**) derivatives via Horner-Emmons reaction, analogous to synthesis of 4-benzylpiperidine (**45**) derivatives

vary significantly using the same reaction conditions. Using the same method and conditions used to make **45** derivatives from **44**, the reactions of **36** with *N*-Boc-3-piperidone (**39**) were observed to take much longer at room temperature (48 hours instead of 16 hours for synthesis of **45** derivatives, and longer for reactions with *N*-Boc-3-pyrrolidinone **54** which typically did not go to completion). In contrast to the reactions with **44**, the results indicated that in some cases the hydrolysis of the phosphonate was significantly faster than the Horner-Emmons reaction with *N*-Boc-3-piperidone or *N*-Boc-3-pyrrolidinone, resulting in loss of the phosphonate reagent before complete consumption of the limiting piperidone or pyrrolidinone reagent even when a significant excess is used (see Scheme 11).

For reactions with *N*-Boc-3-piperidone (**39**), using a large excess of **36** and base resulted in the piperidone reagent being completely consumed in most cases. Despite this, the yields of product **67** after column chromatography were consistently low, potentially indicating that these derivatives are not effectively isolated and purified by the same work-up procedure (Table 12). The reasons for this have not been identified, but the amount of crude product before column chromatography combined with NMR analysis of this crude mixture anticipated a higher expected yield which was not collected, potentially indicating that interactions with the column during chromatographic separation resulted in loss of product. It was observed that while these derivatives had similar R_f values to the corresponding 4-substituted piperidine derivatives (**45**), attempts to purify the products by column chromatography on silica gel were hindered by the seemingly stronger interactions of the compounds with the silica, and yielded significantly more dilute fractions. From the observations and low yield obtained, it was considered possible that the products did not completely elute from the column, even when more polar elution solvents were used.

The Horner-Emmons reaction gave predominantly the *E*-isomer of **67**. The favourable formation of the *E*-isomer is expected from the Horner-Emmons reaction, as the reaction progresses through a less sterically-hindered intermediate in a conformation with the bulky benzene ring and Boc-protecting group on opposite sides, resulting in the *E*-isomer product. The NMR signals corresponding to each isomer were identified using 2D NMR experiments (Figure 43), and the ^{1}H NMR spectrum signals were integrated to obtain the relative proportion of each isomer in the mixture. The signals corresponding to atoms in the piperidine ring were typically broadened due to slow rotation of the Boc-protecting group and some ^{13}C NMR

Table 12: Combined yield and (*E*/*Z*)-selectivity of Horner-Emmons reaction for synthesis of 3-benzylidenepiperidine derivatives (**67**). (*E*/*Z*)-Isomer ratio was determined by comparing integration of ^{1}H NMR signals. * Denotes signals corresponding to the minor *Z*-isomer.

	R	Combined Yield (%)	(*E*/*Z*)-Isomer Ratio	δ_H H_A,*H_A (ppm)
67c:	3-CH_3	39	4:1	6.38,6.30
67f:	3-OCH_3	21	7:3	6.39,6.30
67h:	2-F	27	4:1	6.34,6.27
67j:	4-F	23	7:3	6.36,6.27
67x:	H	47	7:3	6.40,6.33

signals adjacent to the nitrogen atom were so broad they were not observed. The slow rotation also affected the appearance of the alkene hydrogen signal, as in the *E*-isomer the Boc-protecting group is closer in space which results in the observed broadness of the signal. In all cases the broader alkene hydrogen signal of the major *E*-isomer appeared downfield of the *Z*-isomer alkene signal in the ^{1}H NMR spectrum, and HSQC experiments were used to determine the shifts of the broad ^{13}C NMR signals which were difficult to assign unambigously otherwise.

In an attempt to reduce any significant loss of intermediate compounds by column chromatography, the alternate method for Boc-deprotection using hydrogen chloride solutions was investigated (Scheme 37). This deprotection method had been mentioned in the literature preparation of 3-benzylpiperidines, and was expected to give a solid hydrochloride product **38** which could be collected by filtration from the crude reaction mixture and therefore avoid any need for column chromatography to purify **67** or the hydrogenation product **69** before the deprotection step.[59] This was attempted for the unsubstituted derivative **38x** and the methyl-substituted derivative **38c**, however using the same method used to make the 4-benzylpiperidine derivatives yielded no precipitated product in the final step of the method. As an alternate strategy, the hydrogenation products **48x** and **48c** were purified prior to the deprotection step, and the solvent was evaporated from the deprotection reaction mixture. It was found that the hydrochloride salts of the 3-benzylpiperidine derivatives, unlike the 4-benzylpiperpdine hydrochlorides, were not solids: although the reaction was successful, the product could not be collected by filtration from the hydrogen chloride solution, and therefore did not offer any advantage over the TFA deprotection method.

As a further attempt to isolate workable quantities of these 3-benzylpiperidine compounds, the alternate Heck reaction to make **67x** was investigated. This pathway first required the Wittig reaction of *N*-Boc-3-piperidone to synthesise the alkene **70**, followed by palladium-catalysed coupling with bromobenzene to give the desired piperidine **67** (Scheme 38). It was found that the Wittig reaction conditions used to synthesise 4-methylidenepiperidine **66** (81%

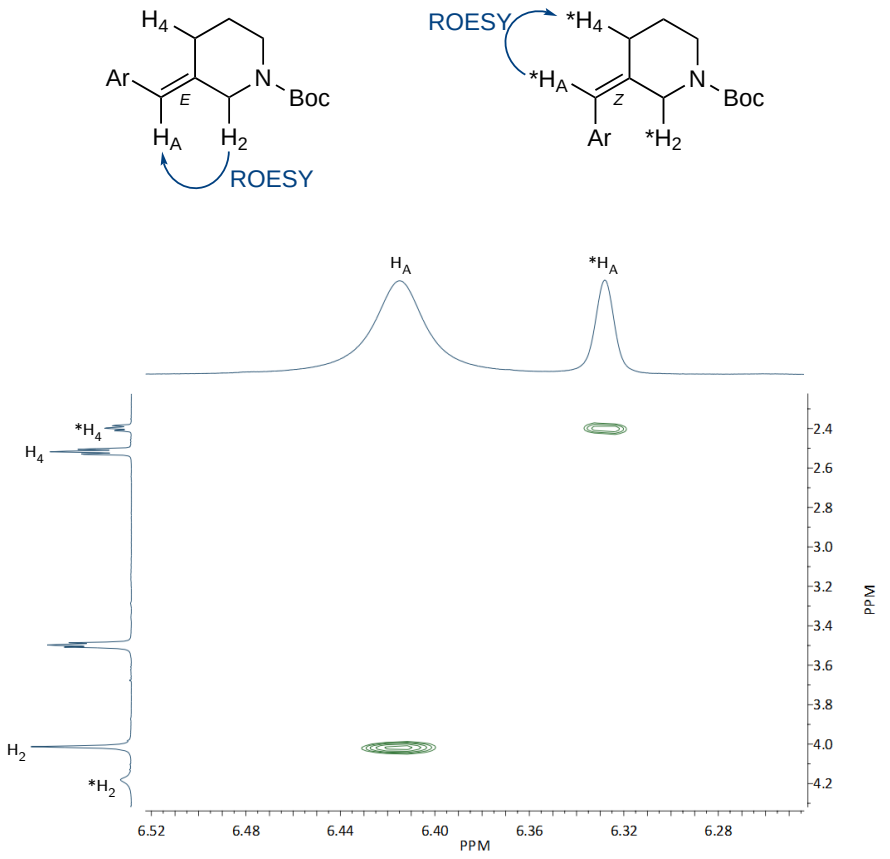
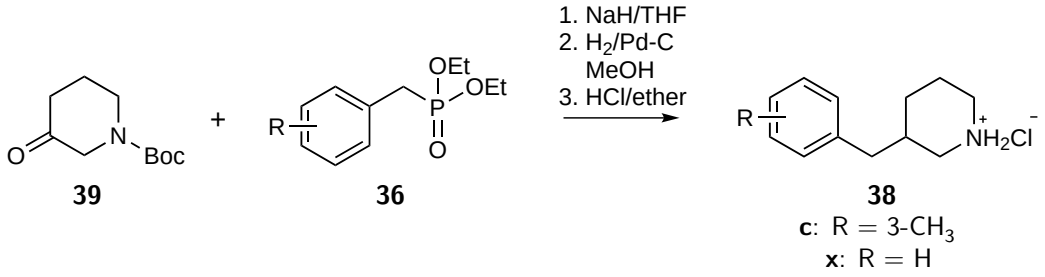


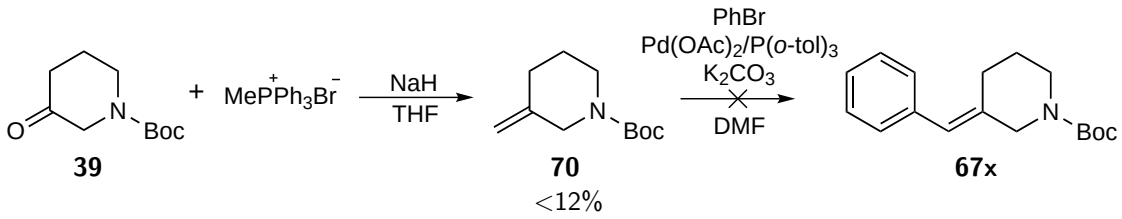
Figure 43: ROESY correlations showing ^{1}H NMR signals corresponding to the *E*- and *Z*-isomers of *N*-Boc-3-benzylidenepiperidine products (**67**). ROESY spectrum shown corresponds to Ar = Ph derivative, **67x**.



Scheme 37: Attempted 3-step synthesis of 3-benzylpiperidine hydrochloride salts (**38**) via a Horner-Emmons reaction, analogous to synthesis of 4-benzylpiperidine derivatives (**49**).

yield, see Scheme 35) were not as successful in the synthesis of **70**. A range of conditions were attempted in the synthesis of this product, but only very low yields were obtained and the product could not be completely purified from the triphenylphosphine oxide by-product. The ^{1}H NMR spectrum of the asymmetric product **70** had alkene signals at 4.75 ppm and 4.81 ppm and the signals consistent with the Boc-protected piperidine ring. The yield, even impure, was very low compared to the yields achieved using the alternate Horner-Emmons reaction pathway.

Following the preparation of the reagent, the Heck reaction conditions used to make **45x** from



Scheme 38: Attempted synthesis of Boc-protected 3-benzylidenepiperidine (**67x**) via a Wittig and Heck reaction pathway.

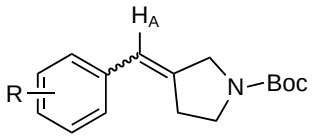
bromobenzene and **66** (see Scheme 35) were then unsuccessfully applied to the attempted synthesis of **45x** from bromobenzene and the crude **70**. A comparison of the crude ^{1}H NMR spectrum from the Heck reaction mixture with the data from the isolated product **67x** from the Horner-Emmons reaction clearly demonstrated that the product alkene was not present in the mixture. The clearest indication that no product was present in the mixture was the absence of the alkene hydrogen signals at 6.33 and 6.41 ppm, which each correspond to the *E*- and *Z*-isomers of the desired product. Instead, the ^{1}H NMR spectrum of the reaction mixture contained signals corresponding to the reagents only. Due to the low yielding synthesis of the methylidenepiperidine **70** and the ineffective Heck reaction conditions, this method was not pursued further.

From this investigation it was determined that the Horner-Emmons method was the most effective method to synthesise these derivatives of **67**, but due to the very low yields the full range of 3-piperidine derivatives (analogous to the range of 4-piperidine derivatives, **45**) were not synthesised in this work. The compounds that were made and successfully purified from the Horner-Emmons reaction were deemed sufficient to compare the difference between the benzylpiperidine-type compounds, and ultimately to assess whether the change in benzylpiperidine shape will impact the binding of the target benzylpiperidine-extended aminoquinoline ligands with the Tec SH3 domain.

Following the attempted Horner-Emmons reactions with *N*-Boc-3-piperidine, the analogous synthesis of **68** derivatives by the Horner-Emmons reaction of *N*-Boc-3-pyrrolidine **54** and **36** derivatives was also found to be low yielding (Scheme 36) but some required derivatives were successfully isolated in workable quantities (Table 13).

In contrast to synthesis of the 3-benzylpiperidine derivatives the selectivity for the *E*-isomer was not observed, and the mixture of products was shown by integration of the ^{1}H NMR signals to contain the two alkene isomers in approximately equal concentrations. The ROESY NMR experiment did not identify correlations between the alkene signals and any pyrrolidine ring hydrogen signals and therefore the signals corresponding to each isomer could not be definitively assigned: the shape of the flattened five-membered ring could mean weaker correlations are observed, and the broadness of the ^{1}H NMR signals may also contribute to the lack of observed ROESY correlations. By use of other 2D NMR experiments — specifically

Table 13: Yields of Boc-protected 3-benzylidenepyrrolidine derivatives (**68**) by Horner-Emmons reaction. The stereochemistry of the major isomer could not be unambiguously assigned using 2D NMR experiments.



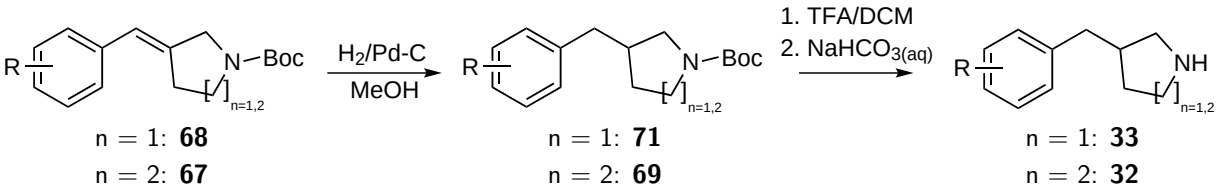
(*E*/*Z*)-**68**

	R	Combined Yield (%)	Isomer ratio	δ_H H_A (ppm)
68c:	3-CH_3	2	11:9	6.26,6.33
68h:	2-F	8	11:9	6.23,6.29
68i:	3-F	4	1:1	6.27,6.35
68x:	H	10	1:1	6.25,6.33

COSY, HSQC and HMBC experiments — the correlations could be used to determine which of the signals corresponded to each isomer, and therefore determine that the signals were consistent with the expected structures even though stereochemistry could not be assigned.

Hydrogenation of the 3-substituted piperidines (*E*/*Z*-**67**) and 3-substituted pyrrolidines (*E*/*Z*-**68**) yielded the corresponding **69** or **71** derivative (Scheme 39). Characterisation of the 3-piperidine products was hindered by the broadness of the signals in the NMR spectra, although this feature is indicative of a Boc-protected piperidine ring and shows the changes in ring conformation are slow on the NMR timescale. HRMS analysis of the purified products and integration of the ^{1}H NMR signals were consistent with the target structures, but broadness and overlap of the ^{13}C NMR signals meant unambiguous assignment of all NMR signals was not possible - it was anticipated that the subsequent Boc-deprotection step would resolve the factor of slow conformation change of the piperidine ring, and therefore enable better characterisation of the 3-piperidine products. In contrast, the NMR signals of the 3-pyrrolidine products were not as significantly broadened, and splitting of the piperidine ring signals in the ^{1}H NMR spectrum (and the ^{13}C NMR spectrum when the molecule contained a fluoro-substituent) was evident. Each pyrrolidine hydrogen atom had is own distinct signal in the ^{1}H NMR spectrum, indicating a substantial change in shape of the pyrrolidine ring occurred as a result of hydrogenation of the alkene. Each of the products was obtained from the hydrogenation reaction with a high yield (Tables 14 and 15).

TFA-catalysed deprotection of the derivatives of **69** and **71** yielded the corresponding 3-piperidine and 3-pyrrolidine derivatives (**32** and **33** respectively) with good yields (Tables 14 and 15), with success of reaction clearly demonstrated by loss of the protecting group signals in the NMR spectra and corresponding mass loss in the HRMS analysis of the product samples. The complete removal of residual TFA catalyst was confirmed using ^{19}F NMR



n = 1: **68** n = 2: **67** | n = 1: **71** n = 2: **69** | n = 1: **33** n = 2: **32**

Scheme 39: General synthesis of 3-benzylpiperidine (**32**) and 3-benzylpyrrolidine (**33**) derivatives by hydrogenation and Boc-deprotection.

Table 14: Yields of 3-benzylpiperidine derivatives from hydrogenation and Boc-deprotection of benzylidenepiperidines **67**.

	R	Yield 69 (%)	Yield 32 (%)
c:	3-CH_3	100	98
f:	3-OCH_3	100	95
h:	2-F	70	92
j:	4-F	97	92
x:	H	100	96

Table 15: Yields of 3-benzylpyrrolidine derivatives from hydrogenation and Boc-deprotection of benzylidenepyrrolidines **68**.

	R	Yield 71 (%)	Yield 33 (%)
h:	2-F	99	33
x:	H	100	100

spectroscopy. For the 3-piperidine derivatives, the broadness in the ^{1}H NMR signals of the precursor was not observed in the deprotected product, and signals with splitting and coupling constants consistent with a more chair-like piperidine structure were present. Distinct axial and equatorial hydrogen signals were observed, and a substantial upfield shift of the equatorial hydrogen atoms adjacent to the piperidine nitrogen was also observed due to loss of the carbonyl of the protecting group. For the 3-pyrrolidine products, only small differences in the NMR data were observed compared to the Boc-protected precursor. The signals corresponding to the protecting group were no longer present, but the chemical shifts and appearance of other signals in the ^{1}H and ^{13}C NMR spectra were largely unchanged, indicating the 5-membered heterocyclic ring was substantially less affected by the planarised Boc-protecting group.

Synthesis of pyridinylmethylpiperidines

While Horner-Emmons reactions were also the preferable pathway for the synthesis of pyridinyl-extended piperidines (Pathway 1, Figure 44), the poor yielding synthesis of the phosphonate **50c** indicated that other pathways may be more viable. Given that a relatively simple synthesis of phosphonium salts **52** was achieved, the Wittig reaction pathway (Pathway 2) would be more viable for the synthesis of **53** derivatives if higher-yielding reaction conditions with

N-Boc-4-piperidone and an effective work-up procedure to separate the triphenylphosphine oxide by-product (**72**) could be found. The Heck reaction pathway (Pathway 3) was also considered because the synthesis of the intermediate **73** had already been achieved, and therefore reaction of a bromopyridine instead of bromobenzene in the Heck reaction would yield the required products. All three of these methods were attempted to determine whether an effective pathway for synthesis of pyridinylmethylpiperidines could be achieved.

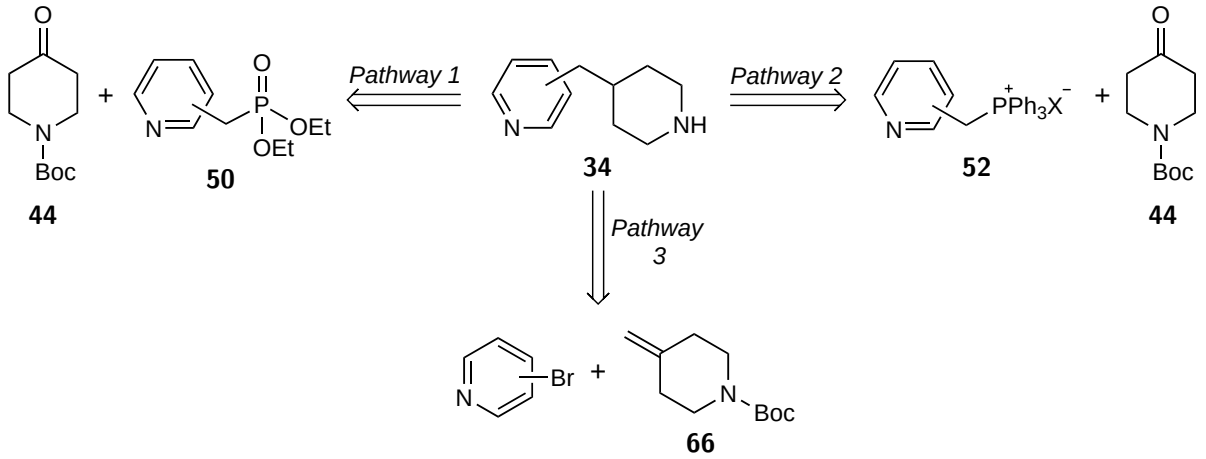
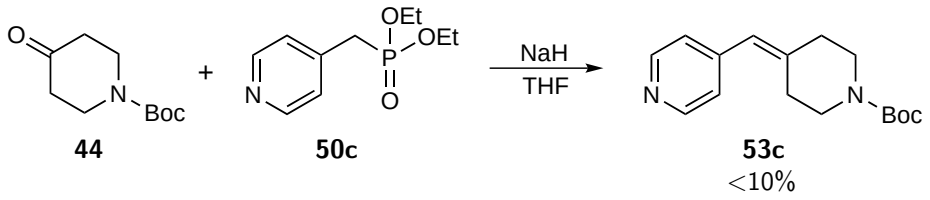


Figure 44: Proposed retrosynthesis of pyridinyl-extended piperidines (**34**).

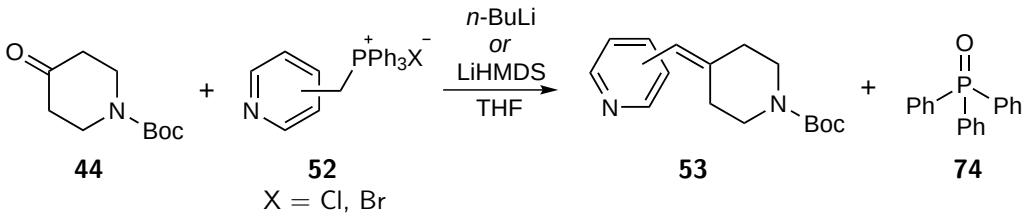
The Horner-Emmons reaction of impure **50c** (see Scheme 19) with Boc-protected piperidone **44** and sodium hydride was attempted (Scheme 40). As observed in the ^{1}H NMR spectrum of the crude reaction mixture, some desired product **53c** was formed alongside undesired side-products. Distinct ^{1}H NMR signals showing successful synthesis of the desired alkene product were observed, including the singlet at approximately 6.3 ppm for the alkene hydrogen and the series of broad signals consistent with the Boc-protected 4-piperidine ring. A large amount of unreacted piperidone reagent was also recovered. None of the products could be isolated and characterised due to the small scale of the reaction and the number of impurities present. Given the poor yield of the Horner-Emmons reaction and the unreliable synthesis of the required phosphonate, this was not a viable method for synthesis of the target pyridinyl-extended piperidine compounds.



Scheme 40: Attempted synthesis of a pyridinyl-extended piperidine derivative (**53c**) via a Horner-Emmons reaction of piperidone **44** and pyridinyl-extended phosphonate **50c**.

The Wittig reaction was potentially a more viable method as the phosphonium salts (**52**) had been easier to synthesise and isolate. Wittig reactions using *n*-BuLi or LiHMDS as the

base were successful in achieving the desired products (Scheme 41). In most cases addition of base to the phosphonium salt caused a colour change of the mixture to bright orange or red, but for the reaction of **52c** the mixture turned a dark red/black colour when either *n*-BuLi or LiHMDS were added. The different colour of that particular reaction potentially indicated that some degradation or unknown side-reaction had occurred, however no further compounds were present in sufficient quantities to be isolated even though ^{1}H NMR analysis of the crude mixture demonstrated that a more complex mixture of compounds was present. For all target products **53(a-c)**, spectroscopic analysis was used to clearly demonstrate the alkenes were successfully synthesised and isolated. The characteristic broad singlet signal for the alkene in the ^{1}H NMR spectrum was observed in each case, and the broad signals for the Boc-protected piperidine were observed in both the ^{1}H and ^{13}C NMR spectra, directly comparable to the spectra for the benzylpiperidines previously prepared.



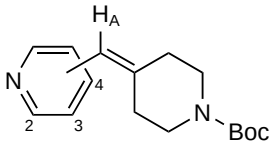
44 **52** X = Cl, Br **53** **74**

Scheme 41: General synthesis of pyridinyl-extended 4-piperidine derivatives (**53**) via Wittig reaction.

Initially, it was found that very low yields were recovered from the reaction work-up despite complete consumption of the reagent piperidone. As the work-up required a liquid-liquid extraction and these compounds were expected to be more water-soluble than the benzylpiperidine analogues, the work-up was amended to avoid liquid-liquid extraction. The mixture was instead quenched with water and concentrated to dryness under reduced pressure, then suspended in a solvent mixture (3:1 hexane/ethyl acetate) and filtered before column chromatography. This filtration removed the water-soluble impurities and also removed some of the by-product of the reaction, triphenylphosphine oxide (**74**). The residual impurities were successfully removed by column chromatography to give the desired products in low-moderate yields (Table 16).

The same method was used to synthesise 3-(2-pyridinylmethyl)piperidine in moderate yield (Scheme 42). As with the 3-benzylidenepiperidine derivatives synthesised by a Horner-Emmons reaction mechanism, the Wittig reaction showed some selectivity for the *E*-isomer, but the NMR data demonstrated that this was less significant as the ratio of products was determined to be 5:4, by integration of the alkene signals in the ^{1}H NMR analysis. Similar to the previous 3-benzylidenepiperidine derivatives, the NMR signals of the two isomers were substantially broadened and many were overlapping in both the ^{1}H and ^{13}C NMR spectra which made determination of chemical shift and unambiguous assignment of all signals difficult, although correlations in 2D NMR experiments were used to assign signals to their respective

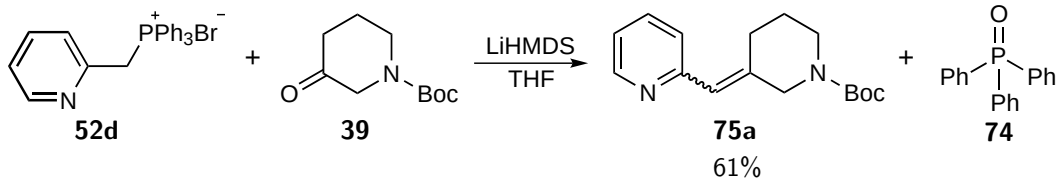
Table 16: Results of Wittig reactions to give pyridinyl-extended piperidine derivatives (**53**).



53

	Pyridinyl substitution	Yield (%)	δ_H H_A (ppm)
53a:	2	81	6.37
53b:	3	36	6.30
53c:	4	53	6.28

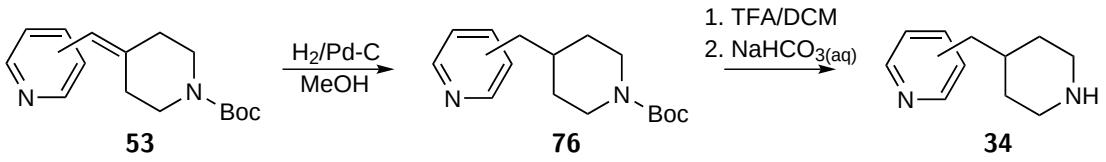
isomer. As with all other benzylidenepiperidines, there were not distinct axial and equatorial hydrogen signals in the ^{1}H NMR spectum, indicating the piperidine ring is substantially planarised due to the alkene.



Scheme 42: Synthesis of a Boc-protected 3-pyridinylmethylidenepiperidine derivative (**75a**) via Wittig reaction of **52d** and piperidone **39**.

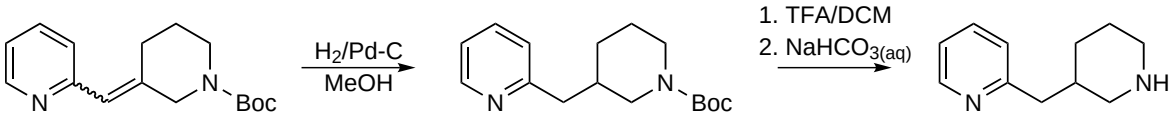
Each of the alkene products, **53(a-c)** and **75a**, were converted to the required piperidines by hydrogenation and deprotection with TFA under standard conditions as previously described for the 4-benzylpiperidine derivatives (Schemes 43, 44). Characteristic chemical shift differences were observed in the NMR spectra in each case to demonstrate the reaction was successful, as described for benzylpiperidines previously: loss of the alkene signals and presence of distinct but broad axial and equatorial piperidine ring signals were observed for hydrogenation product, and after the subsequent Boc-deprotection reaction the signals corresponding to the protecting group were no longer present and the ^{1}H NMR signals for the equatorial hydrogens adjacent to the piperidine ring were significantly upfield compared to the Boc-protected compound (Table 17). The yields of each piperidine varied due to the water solubility which reduced the recovery of the piperidine product during work-up of the deprotection reaction, and one derivative, **34b**, could not be recovered from the reaction mixture.

Due to the lack of reliability in the Horner-Emmons and Wittig reactions used to synthesise derivatives of **53**, the Heck reaction was also investigated as a potential pathway to pyridinyl derivatives (see Pathway 3, Figure 31). The same Heck reaction conditions which gave



53 **76** **34**

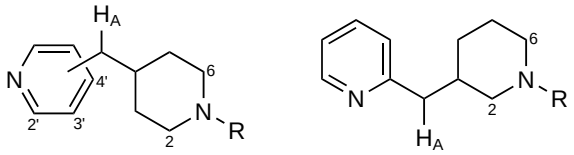
Scheme 43: General synthesis of pyridinylmethylpiperidine derivatives (**34**) by hydrogenation and Boc-deprotection of the corresponding methylidenepiperidines **53**.



75a **77a** 100% **35a** 84%

Scheme 44: Synthesis of 3-(2-pyridinylmethyl)piperidine (**35a**) via hydrogenation and Boc-deprotection.

Table 17: Yields of 4-pyridinylmethylpiperidine derivatives (**34**) from the corresponding alkenes (**53**) over two steps.



76,**34** **77**,**35**

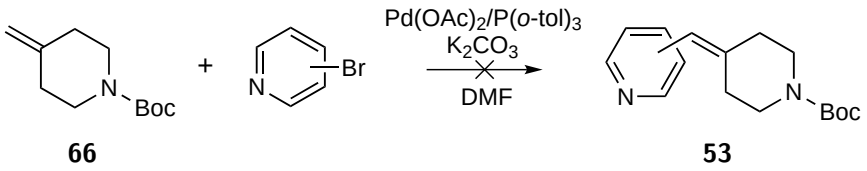
	Pyridinyl substitution	δ_H H_A (ppm)	δ_H $H_{(2/6)eq}$ (ppm)		δ_H $H_{(2/6)eq}$ (ppm)	Yield (%)
76a:	2'	2.71	4.07	**34a:**	3.26	41
76b:	3'	2.55	4.08	**34b:**	-	0
76c:	4'	2.53	4.08	**34c:**	3.05	59
77a:	2'	2.66/2.72	3.89	**35a:**	3.25	84

some 4-benzylidenepiperidine **45x** (see Scheme 35) were attempted using 2-bromopyridine or 3-bromopyridine, however no product **53a** or **53b** was observed in the reaction mixture and only reagents were recovered (Scheme 45). A range of palladium-catalysed conditions were tested but no formation of product was observed in any case, and this method was not deemed viable compared to the Wittig reaction pathway which yielded the desired products.

2.3.4 Synthesis of 6-position substituted 2-chloroquinolines: Selective Buchwald-Hartwig coupling

Synthesis of 6-bromo-2-chloroquinoline

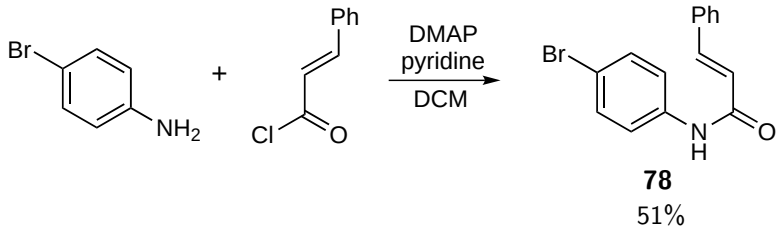
After the piperidine compounds, the key intermediate required for the synthesis of the



Scheme 45: Attempted synthesis of 4-pyridinylmethylpiperidine derivatives (**53**) via Heck reaction of **66** with bromopyridines.

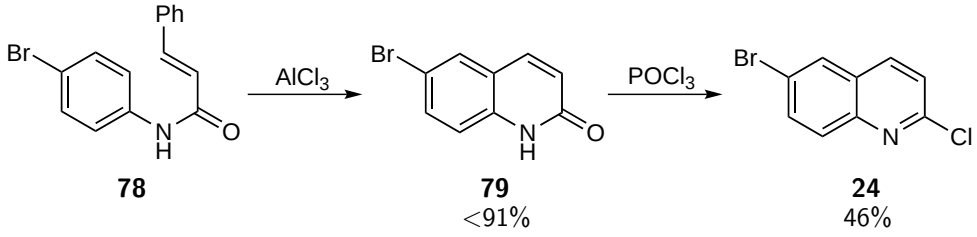
6-position substituted 2-aminoquinolines is 6-bromo-2-chloroquinoline **24**. The two halide substituents are necessary in order for the successive amination reactions to occur under Buchwald-Hartwig conditions to yield the extended 2-aminoquinolines. A literature method for synthesis of **24** had been reported previously and was utilised in this work; the three-step synthesis from commercially available starting materials was reported to give **24** with reasonable yield.[76]

By this literature method, cinnamanilide **78** was prepared from 4-bromoaniline and cinnamoyl chloride with moderate yield (Scheme 46). The NMR spectra of the product were consistent with literature reporting of the compound, showing the distinctive ^{1}H NMR *trans*-alkene signals with a large coupling constant ($^{3}J_{H,H}$ = 15.5 Hz) and *para*-substituted benzene ring signals indicating the successful reaction.



Scheme 46: Synthesis of cinnamanilide intermediate **78** via a literature method.[76]

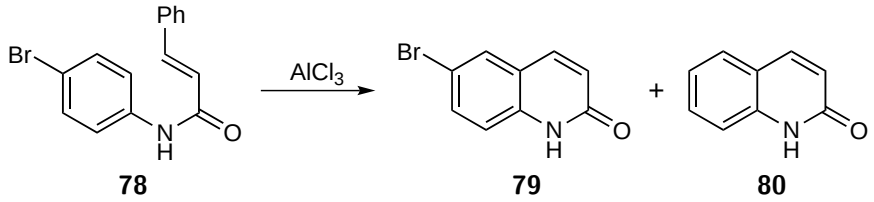
By the literature method, ring closure to give the quinolone **79** was achieved with a Friedel-Crafts acylation as a melt reaction, and subsequent reaction of the product with phosphorous oxychloride ($POCl_3$) gave the required 2-chloroquinoline **24** (Scheme 47).



Scheme 47: Synthesis of 6-bromo-2-chloroquinoline (**24**) from prepared cinnamanilide (**78**) via literature method.[76]

The melt reaction of **78** with $AlCl_3$ had variable results, and the reaction success was highly dependent on the quality of the $AlCl_3$ used. Successful synthesis of **79** (Scheme 48) was

observed by the loss of the *trans*-alkene ^{1}H NMR signals with a large coupling constant and instead signals with a smaller alkene coupling constant ($^3J_{H,H}$ = 9.5 Hz) were observed to indicate the ring-closing reaction was successful, but another similar product was often formed and reduced the yield of **79** obtained. The ^{1}H NMR spectrum of the side-product showed distinctive triplet signals which would not be observed for a 2,6-substituted quinolone product such as **79**, however the side-product appeared to also be the product of the ring-closure reaction as signified by the two doublets with a coupling constant of $^3J_{H,H}$ = 9.5 Hz at similar shifts to those observed for **79** (Figure 45). Instead of the splitting pattern of doublets with both larger $^3J_{H,H}$ and smaller $^4J_{H,H}$ coupling constants observed for **79** (8.7 Hz and 2.1 Hz respectively), there was an additional hydrogen signal observed in the ^{1}H NMR spectrum for the side-product, and the presence of two triplet and doublet signals coupling to each other with a different coupling constant ($^3J_{H,H}$ = 7.7 Hz) indicated the bromide had been lost to give **80**.



78 **79** **80**

Scheme 48: Synthesis of side product **80** in attempted synthesis of **79** by reaction of $AlCl_3$ with cinnamanilide. Approximate ratio of products determined from crude ^{1}H NMR spectrum varied from 1:4 to 1:1, favouring **79**.

The formation of the undesired side-product appeared to be dependant on the purity of the $AlCl_3$ used and exposure of the reagent mixture to atmospheric moisture when handled, which would cause degradation of $AlCl_3$ to $Al(OH)_3$. Although air exposure was not eliminated, the relative quantity of **80** produced could be minimised by using $AlCl_3$ which had not been exposed to air prior to mixing with the reagent **78**. While small amounts of **80** were sometimes still present in the reaction mixture, this product was removed in the work-up after reaction with phosphorous oxychloride.

Reaction of **79** with $POCl_3$ proceeded to give the required quinoline intermediate **24**, which precipitated from the reaction and was purified by recrystallisation. The successful conversion to this product was demonstrated by analysis of the ^{1}H NMR spectrum which showed loss of the broad NH signal from the quinolone, and a significant downfield shift for the H_3 signal consistent with that reported in literature.[77] Slow crystallisation of the filtrate from the reaction work-up yielded 2-chloroquinoline, which was formed due to reaction of **80** (an impurity from the previous reaction) with $POCl_3$.

Synthesis of 6-substituted 2-chloroquinolines via Buchwald-Hartwig Amination

The Buchwald-Hartwig amination conditions used to synthesise a range of 6-heterocyclic 2-chloroquinolines had been investigated previously and effectively applied to the synthesis of

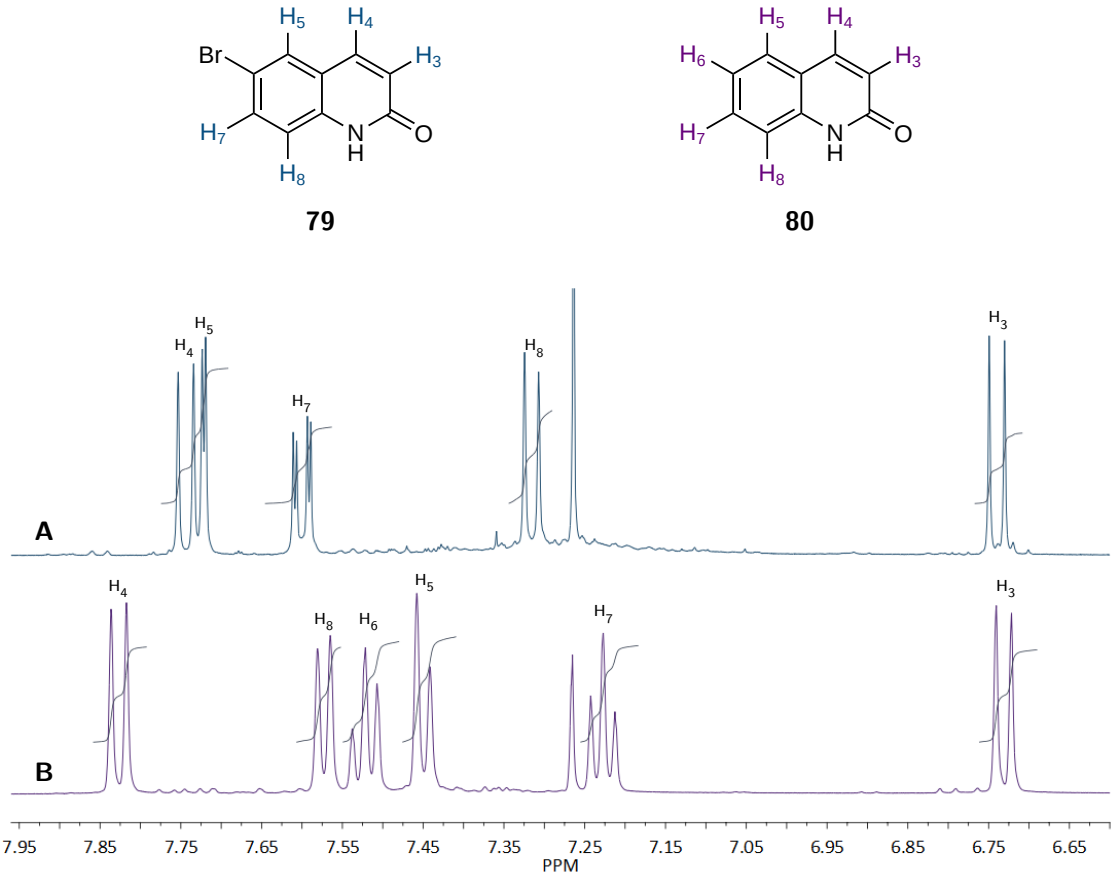
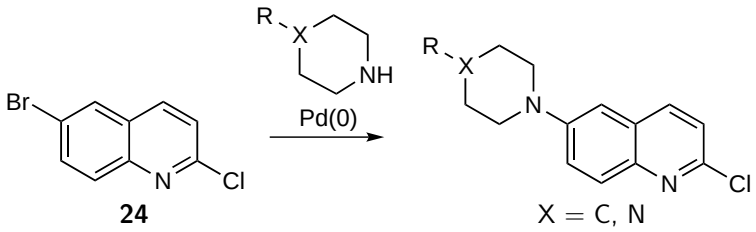


Figure 45: Comparison of ^{1}H NMR spectra for products obtained from Friedel-Crafts acylation with aluminium trichloride. A: Expected 6-bromoquinolin-2(1*H*)-one product (**79**), and B: side-product quinolin-2(1*H*)-one (**80**). Broad NH signals not shown: appears at 12.21 ppm for product **79**, and 12.36 ppm for side-product **80**.

a range of substituted 2-chloroquinolines with good yield and generalisability to a range of amines including piperidines (Scheme 49).[52]



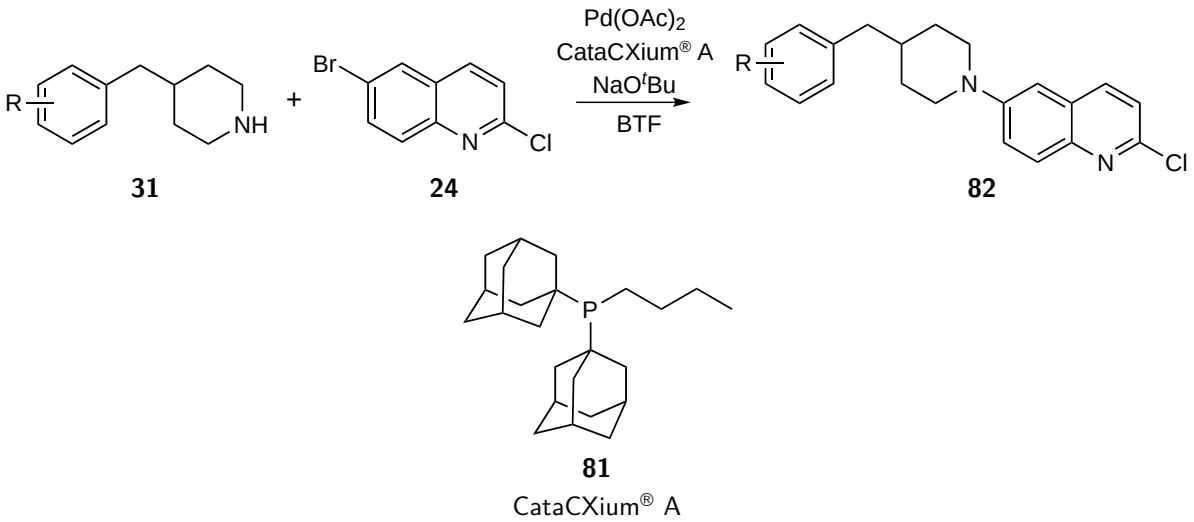
Scheme 49: Previously reported coupling reaction of piperidine derivatives with 6-bromo-2-chloroquinoline (**24**) via Buchwald-Hartwig amination.[52]

The success of the coupling reaction is dependent on the reaction conditions including base, catalyst system, solvent, pressure and temperature. A catalyst system of palladium acetate and CataCXium® A ligand **81** had previously been determined to give the highest yield of the desired products while minimising undesired side-reactions. The base also contributed to the mixture of products obtained: potassium *tert*-butoxide and sodium *tert*-butoxide gave higher yield but use of cesium carbonate as the base resulted in no formation of undesired coupling

side-products.[52]

Best results were achieved in previous work using microwave radiation as a fast and effective method to synthesise the 2-chloroquinolines, and the best alternative method involved heating the reaction mixture in a sealed tube. The solvents used for each of these methods was different, however, because while toluene was used as the solvent in sealed-tube reactions it is not a suitable solvent for microwave reactions, and therefore the similar solvent α,α,α-trifluoromethylbenzene (BTF) was used for microwave-assisted reactions.[78]

In this work, microwave-assisted synthesis was initially attempted for coupling of **24** with **31c**, but a complex mixture of products was observed in the crude reaction mixture and none of the 2-chloroquinoline product could be isolated for characterisation (Scheme 50). In comparison, a sealed-tube reaction using BTF as the solvent instead of toluene gave a much cleaner reaction with no identified side-products. The sealed-tube reactions required a significantly longer reaction time (16 hr, compared to 20-30 minutes for the microwave-assisted method in previous work), but there was more conversion to the desired product rather than side-products so the product could be isolated, therefore sealed-tube reactions were deemed the most effective method for synthesis of the target benzylpiperidine-extended 2-chloroquinoline derivatives. The change of solvent to BTF may have assisted the desired reaction by improving solubility of the reagents, resulting in the apparent success of the sealed-tube reaction method over previously reported results in toluene.

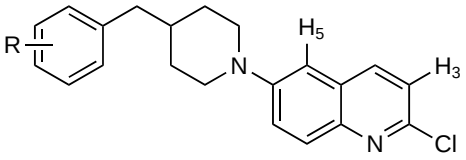


Scheme 50: General synthesis of 6-position substituted 2-chloroquinoline derivatives (**82**) via Buchwald-Hartwig amination. Amination reaction was first unsuccessfully attempted using microwave-assisted conditions, then conducted successfully as sealed-tube reactions.

Using these conditions, the 4-benzylpiperidine derivatives (**31**) were reacted with **24** to give predominately or exclusively the 2-chloroquinoline product with 6-position benzylpiperidine substitution (Table 18). To confirm that the coupling had occurred at the 6-position of the quinoline ring as desired, all significant quinoline and piperidine shifts in both ^{1}H and ^{13}C NMR were analysed compared to the reagents, HRMS data was collected to confirm

the distinctive isotope peaks for a chloro-compound instead of a bromo-compound, and 2D NMR data was collected to determine whether the observed correlations were consistent with the target structure. The ^{1}H NMR spectra showed significant upfield shifts for the H_5 and H_7 signals (typically 1.0 ppm and 0.3 ppm difference respectively) compared to the bromo-substituted reagent **24**, as would be expected if the electron-donating amine had reacted at the 6-position. Comparatively, the H_3 signal had a smaller upfield shift. Similarly, the 2D NMR experiments showed correlations of piperidine ring signals with C_6 and adjacent atoms, instead of to C_2 (Figure 46). Specifically, the [^{1}H,^{13}C]-HMBC spectrum correlations between the C_6 quinoline signal and the signals of the axial hydrogen signals adjacent to the piperidinyl nitrogen atom indicated successful coupling (Figure 46A), and the ROESY data clearly demonstrated coupling had occurred at the 6-position of the quinoline structure as correlation of the equatorial $H_{2'/6'}$ piperidine signals with those of H_5 and H_7 was observed (Figure 46B). Together with the HRMS data showing the mass consistent with the expected **82** derivative, including distinctive chlorine isotope peaks, the spectroscopic results confirmed in each case that the desired product was formed.

Table 18: Results of Buchwald-Hartwig coupling reaction to give 6-position substituted 2-chloroquinoline derivatives with 4-benzylpiperidine substituent (**82**). For purposes of comparison, the ^{1}H NMR chemical shifts for the bromo-substituted reagent **24** were 7.42 ppm for H_3 and 7.99 ppm for H_5.



82

	R	Yield (%)	δ_H H_3 (ppm)	δ_H H_5 (ppm)
82a:	4-^{t}Bu	69	7.25	6.97
82b:	2-CH_3	23	7.26	6.98
82c:	3-CH_3	46	7.25	6.98
82d:	4-CH_3	58	7.26	6.98
82e:	2-OCH_3	53	7.25	6.98
82f:	3-OCH_3	68	7.26	6.97
82g:	4-OCH_3	56	7.26	6.98
82h:	2-F	70	7.25	6.98
82i:	3-F	56	7.26	6.99
82j:	4-F	45	7.24	6.97
82n:	2-CF_3	32	7.26	6.99
82o:	3-CF_3	51	7.26	6.99
82p:	4-CF_3	62	7.25	6.98
82x:	H	75	7.25	6.98

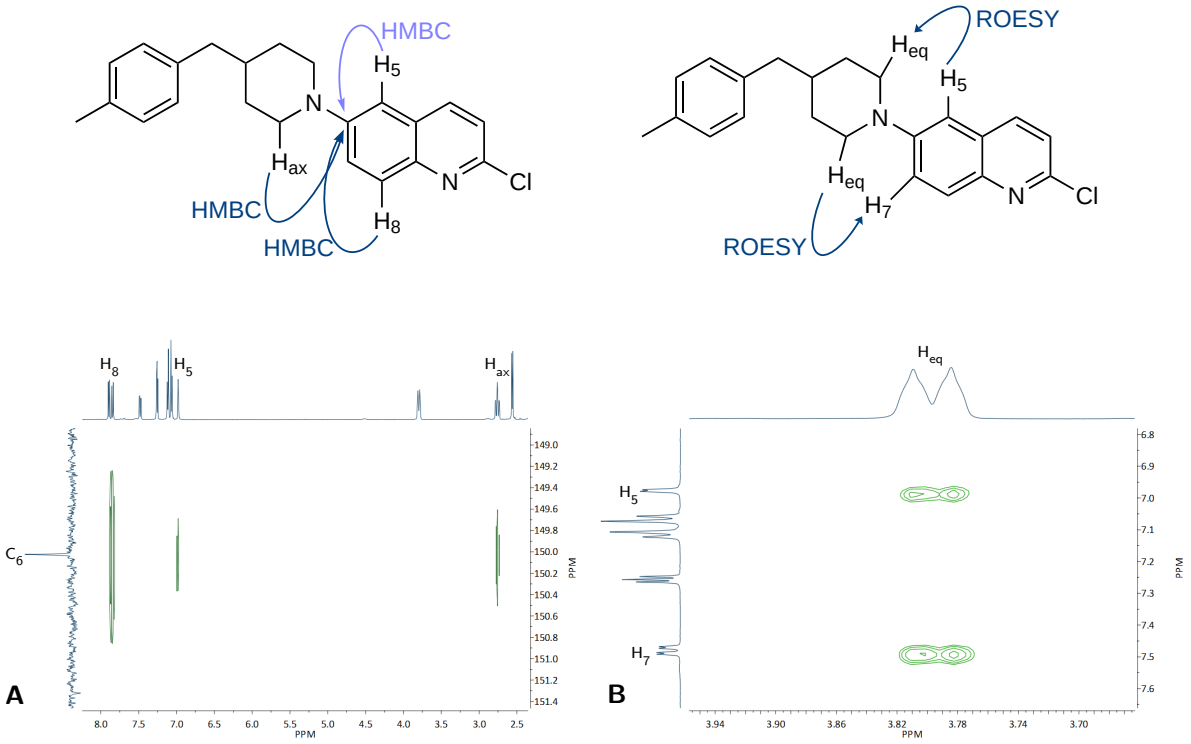
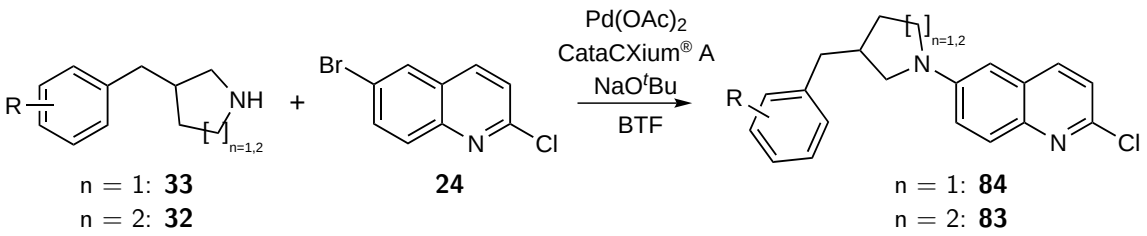


Figure 46: 2D NMR experiments used to determine reaction position from Buchwald-Hartwig amination. A; HMBC correlations with C_6 showing connectivity of piperidine with quinoline ring, and B: ROESY correlations showing correlations between piperidine hydrogen atoms and the quinoline ring demonstrating successful 6-position substitution. Example spectra shown are for 4-methylbenzyl derivative **82d**.

The Buchwald-Hartwig coupling reaction of the 3-benzylpiperidine and 3-benzylpyrrolidine derivatives (**33** and **32** respectively) proceeded with similar results to those observed in the preparation of **82** (Scheme 51, Table 19). Although the yields for the coupling of **33** and **32** with **24** were very varied, in most cases the reaction proceeded and gave the 6-position substituted 2-chloroquinolines as the only product. Similarly to **82** derivatives, the most significant upfield shifts in the ^{1}H NMR spectra for **83** and **84** derivatives corresponded to the H_5 and H_7 signals, which together with consistent shifts in the ^{13}C NMR spectra, 2D NMR experiments, and expected HRMS results confirmed successful coupling at the 6-position of the quinoline.



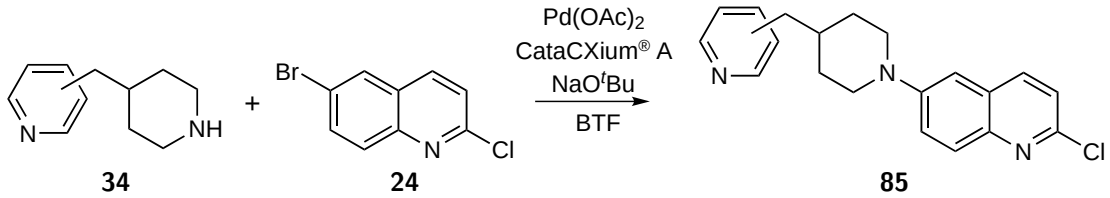
Scheme 51: Synthesis of 2-chloroquinoline derivatives with a 6-position 3-benzylpiperidine or 3-benzylpyrrolidine substituent (**84** and **83**) via Buchwald-Hartwig amination.

The same Buchwald-Hartwig coupling conditions were used to synthesise a methylpyridinyl-extended 4-piperidine derivative **85a** from **34a** and **24** (Scheme 52). The structure of

Table 19: Results of Buchwald-Hartwig coupling reactions for synthesis of target 6-position substituted 2-chloroquinoline derivatives with a benzylpiperidine-type substituent.

	R	Yield (%)	δ_H H_3 (ppm)	δ_H H_5 (ppm)
3-benzylpiperidines				
83c:	3-CH_3	42	7.26	6.92
83h:	2-F	54	7.25	6.93
83j:	4-F	36	7.25	6.91
83x:	H	32	7.25	6.90
3-benzylpyrrolidines				
84h:	2-F	44	7.21	6.58
84x:	H	54	7.20	6.56
4-pyridinylmethylpiperidines				
85a:		48	7.25	6.98
85a:		0	-	-
85a:		0	-	-

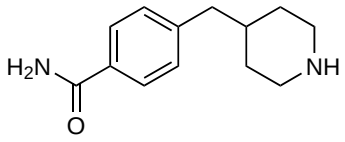
the desired product was confirmed using spectroscopy in the same way as for the previous 2-chloroquinoline derivatives. The synthesis of the other isomers **85b** and **85c** was not achieved using the same method, because the reagents **34b** and **34c** were not isolated in sufficient quantities or with sufficient purity respectively. While the Buchwald-Hartwig aminations were attempted using the reagents despite the low purity or scale, the desired products could not be isolated.



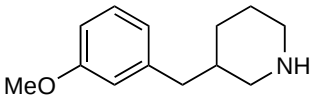
Scheme 52: Synthesis of 2-chloroquinoline derivatives with a 6-position pyridinylmethylpiperidine substituent (**85**) via Buchwald-Hartwig amination.

Investigation of Buchwald-Hartwig reaction products

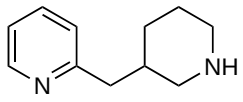
For the benzylpiperidine derivatives utilised in this work, it was determined by NMR analysis that the vast majority of Buchwald-Hartwig coupling reactions did not give other quinoline side-products and the purification of the product was achieved by column chromatography. There were very few exceptions to the highly selective coupling of the piperidine to the 6-position of the quinoline ring. The competing 2-position substitution reaction was favoured when coupling of the piperidines **65c** and **32f** to **24** was attempted, and a further undesired reaction occurred with the attempted coupling of **35a** (Figure 47).



65c



32f



35a

Figure 47: Piperidine compounds for which attempted Buchwald-Hartwig amination reactions with **24** did not yield the target 6-position extended quinoline product.

The only isolated product of the reaction of methoxy-substituted 3-piperidine derivative **32f** and **24** under Buchwald-Hartwig reaction conditions had NMR spectra inconsistent with the expected product **83f**. As demonstrated above, the upfield shift of the H_5 and H_7 signals compared to the starting material **24** is one of the key indicators that the 6-position coupling reaction occurred to give the desired 2-chloroquinoline, and further spectroscopic evidence could be used to conclusively determine that the piperidine has coupled at the 6-position of the quinoline structure. The product from reaction of **32f** did not show such a significant upfield shift for the H_5 and H_7 signals in the ^{1}H NMR spectrum, and instead a large upfield shift was observed for the H_3 signal (6.87 ppm, compared to 7.42 ppm for reagent **24** or 7.26 ppm for the 6-position coupled product **83c**). In addition, the piperidine signals for $H_{2'eq}$ and $H_{6'eq}$ adjacent to the piperidine nitrogen were significantly deshielded compared to derivatives of **83** (4.34/4.36 ppm, compared to 3.67/3.72 ppm for **83c**). These results are consistent with coupling at the 2-position of the quinoline ring, as the electron donating amine substituent would result in the observed increased election density and shielding of the neighbouring H_3 atom, and the proximity of the electronegative quinoline nitrogen to the piperidinyl hydrogen atoms and the quinoline nitrogen would cause the piperidinyl hydrogen atoms to be comparatively deshielded compared to the 6-position coupled piperidine signals.

The 2D NMR experiments also did not show the correlations that would be observed for 6-position substituted quinoline products. Instead, the HMBC experiment showed correlations between the equatorial $H_{2'}$ and $H_{6'}$ piperidine signals and C_2, and the ROESY experiment also showed correlations between these piperidine signals and the H_3 quinoline signal (Figure 48). HRMS of the isolated product gave the masses corresponding to the two isotopes of the 2-position substituted bromoquinoline product, in equal abundance. Combined, these results show that the 2-position substitution reaction had occurred to give product **87f** instead of the desired product **83f** (Scheme 53).

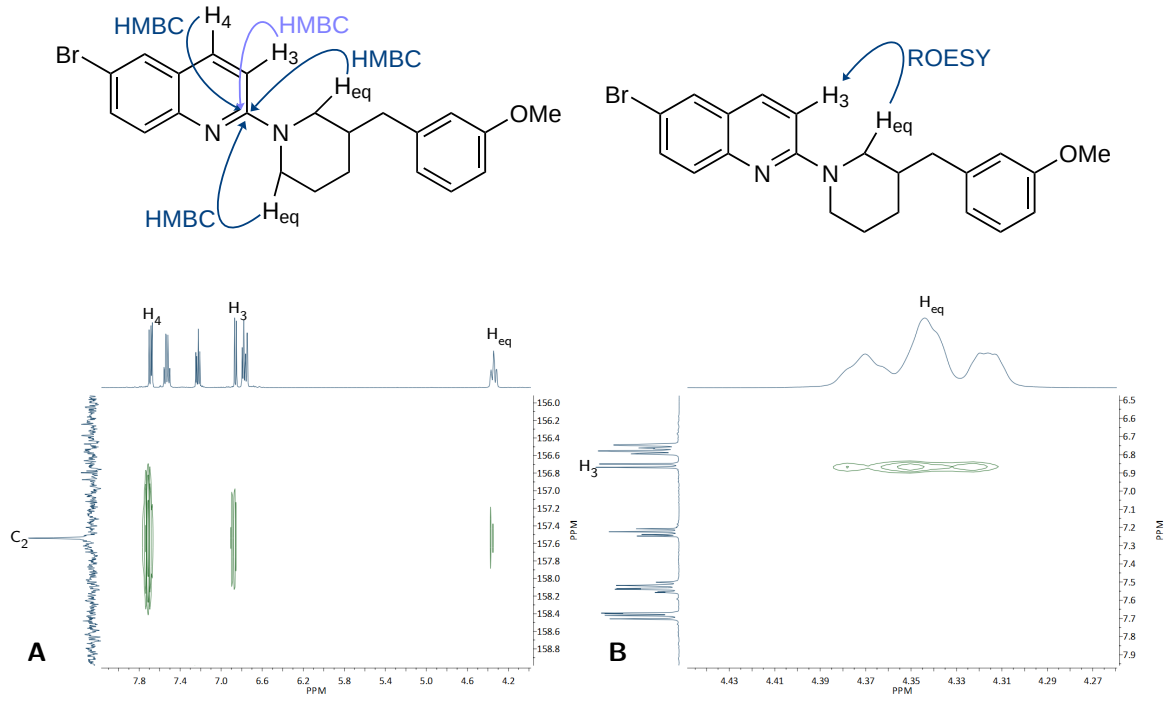
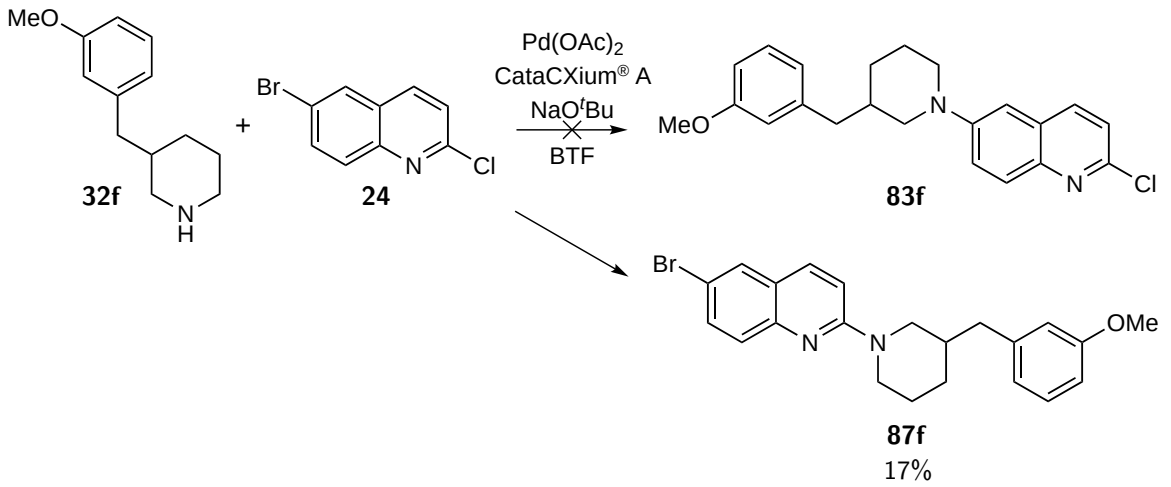


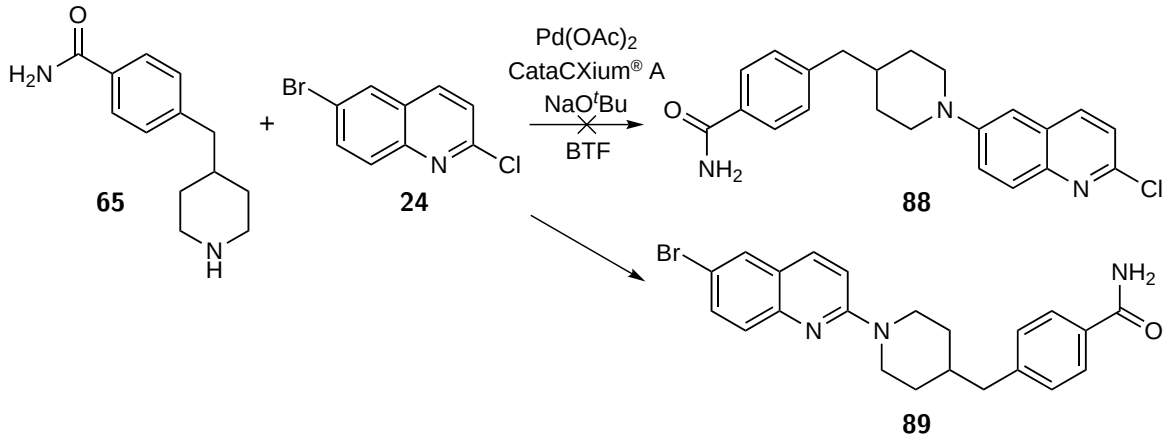
Figure 48: Key 2D NMR experiments used to identify product of Buchwald-Hartwig amination from **32f** and **24**. A: HMBC correlations with C_2 showing connectivity of piperidine with quinoline ring, and B: ROESY correlations showing correlations between piperidine hydrogen atoms and the quinoline ring demonstrating 2-position substitution.



Scheme 53: Attempted synthesis of the 3-benzylpiperidine extended 2-chloroquinoline derivative **83f**, giving only 2-position coupled product **87f**.

Similarly, the attempted Buchwald-Hartwig amination of **65** with **24** resulted in none of the expected 6-position coupled product **88** (Scheme 54). Attempts to purify the reaction mixture were unsuccessful, however ^{1}H NMR analysis of the crude material identified that the mixture contained mostly recovered reagents. While signals corresponding to the target 6-position coupled product **88** were not observed in the spectrum, some signals with shifts and coupling consistent with a 2-position substituted quinoline were observed. These signals for the potential product appeared to be similar to those observed for the 2-position substituted

quinoline **87f** (see Scheme 53). The upfield shift of the H_3 signal indicated that the product likely had an electron-donating substituent at the 2-position of the quinoline ring, and it was therefore postulated that the only coupled product was the result of substitution of the benzylpiperidine reagent to give **89**. Due to the low conversion under these reaction conditions, however, any products could not be isolated and characterised.

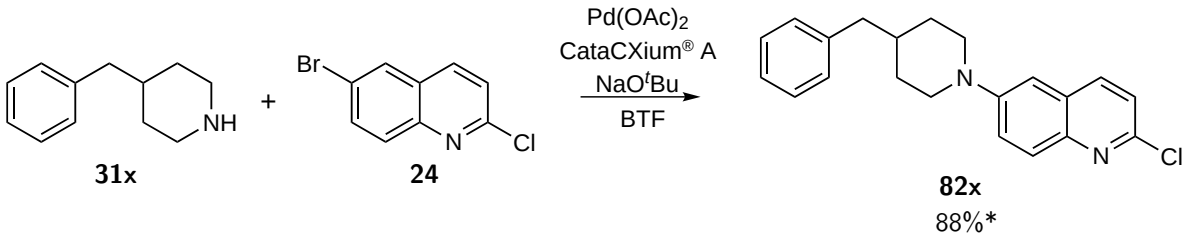


Scheme 54: Attempted synthesis of a 6-substituted 2-aminoquinoline derivative (**88**) which gave the 2-substituted product **89** only.

The absence of any desired 6-position substituted quinoline product in these reactions indicated that some aspect of the conditions was no longer effective with these particular piperidine derivatives. It was hypothesised that the palladium catalyst promoted the highly selective 6-position coupling reaction observed for all other tested benzylpiperidine derivatives, and therefore that solely 2-position substitution in these few cases was the result of these specific piperidine derivatives deactivating or inhibiting the activity of the palladium catalyst. It would be expected that the nucleophilic aromatic substitution reaction of a piperidine at the 2-position aryl chloride of **24** would occur without the need for any catalyst, but whether this substitution reaction would readily occur without an excess of the piperidine reagent and under the sealed-tube reaction conditions in BTF was previously untested. If this nucleophilic substitution reaction of **24** would otherwise occur under the Buchwald-Hartwig conditions used, then the palladium catalyst also serves to prevent this substitution reaction and enable only the desired 6-position coupling reaction.

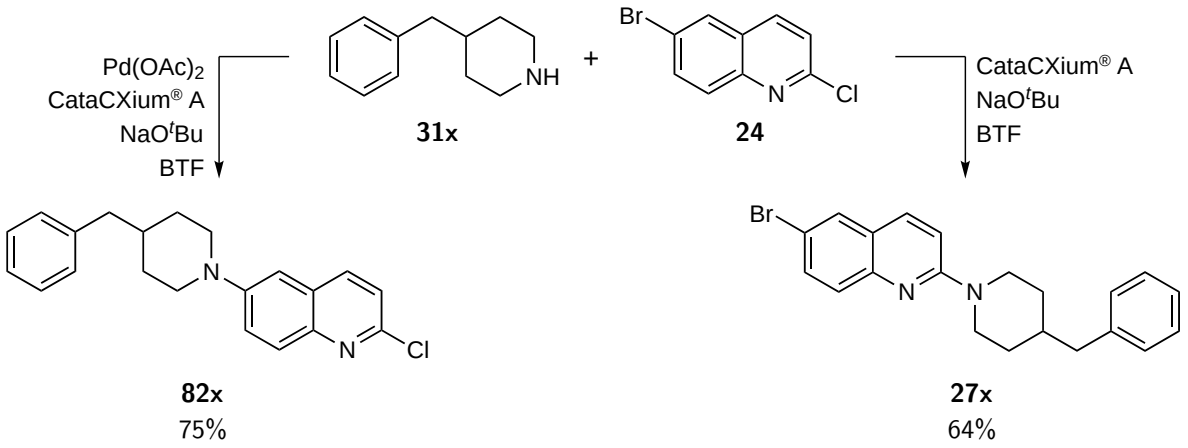
The reaction of **24** and a benzylpiperidine both with and without addition of a palladium catalyst under these sealed-tube reaction conditions had not been attempted previously, but it was proposed that these experiments could be used to test the plausibility of the hypothesis. The selective coupling of unsubstituted 4-benzylpiperidine **31x** with **24** using a Buchwald-Hartwig amination had been reported previously, and was found to selectively give the 6-position coupled quinoline product **82x** (Scheme 55).[52]

As this was reported to give only one product, it was proposed that the reaction of **31x** with **24** could be used to investigate the impact of the palladium catalyst on the production of



Scheme 55: Reported Buchwald-Hartwig amination reaction of 4-benzylpiperidine (**31x**) and 6-bromo-2-chloroquinoline (**24**).[52] *Product not isolated, conversion determined by NMR analysis of crude mixture.

6-position coupled quinoline **82x** or 2-position substitution product **27x**. If the anomalous 2-position substitution products obtained from attempted Buchwald-Hartwig coupling reactions (**89** and **87f**, see Schemes 54 and 53) were a result of inhibited catalyst activity, then it would be expected that the nucleophilic aromatic substitution reaction would occur in the absence of palladium catalyst to give a significant amount of the 2-position substituted quinoline **27x**. Concurrently, it would also be expected that if the palladium catalyst prevents the nucleophilic substutition reaction at the 2-position of the quinoline and enables only the 6-position coupling reaction, then only the 6-position coupled quinoline product **82x** would be observed if the palladium catalyst is present, as previously reported.[52] Both of these experiments were conducted, and the results were consistent with the predictions (Scheme 56).



Scheme 56: Reactions of 4-benzylpiperidine (**31x**) and 6-bromo-2-chloroquinoline (**24**) under Buchwald-Hartwig conditions, with or without addition of the palladium catalyst.

In the absence of palladium catalyst, none of the Buchwald-Hartwig coupling product **82x** was observed or isolated, and instead the only reaction product was **27x**. The identity of the product **27x** was clearly demonstrated by the HMBC and ROESY correlations between the piperidine hydrogen atoms and the quinoline ring which demonstrate the different substitution. In contrast to the NMR spectra of the 6-position substituted products (for example, Figure 46) which show ROESY correlations of equatorial piperidine hydrogen atoms with the H_5 and H_7 doublet signals, the equatorial piperidine hydrogen signals for the product **27x** show a

ROESY correlation with the H_3 signal which is distinguished from the other doublet signals by the larger $^3J_{H,H}$ coupling constant (Figure 49). In addition, the HMBC correlations show the piperidine ring is directly connected to the more deshielded C_2 atom adjacent to the quinoline nitrogen atom. HRMS analysis demonstrated the 6-position bromide substituent was present, as the two product masses were detected due to each major bromine isotopes in equal abundance.

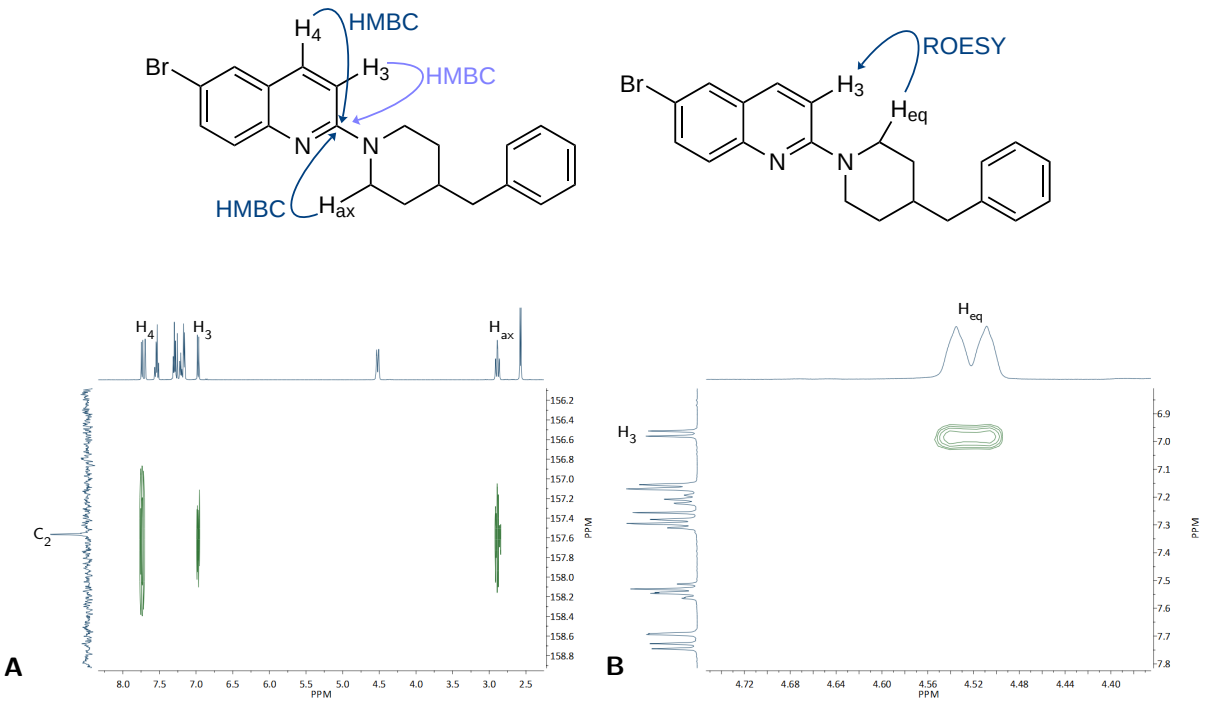
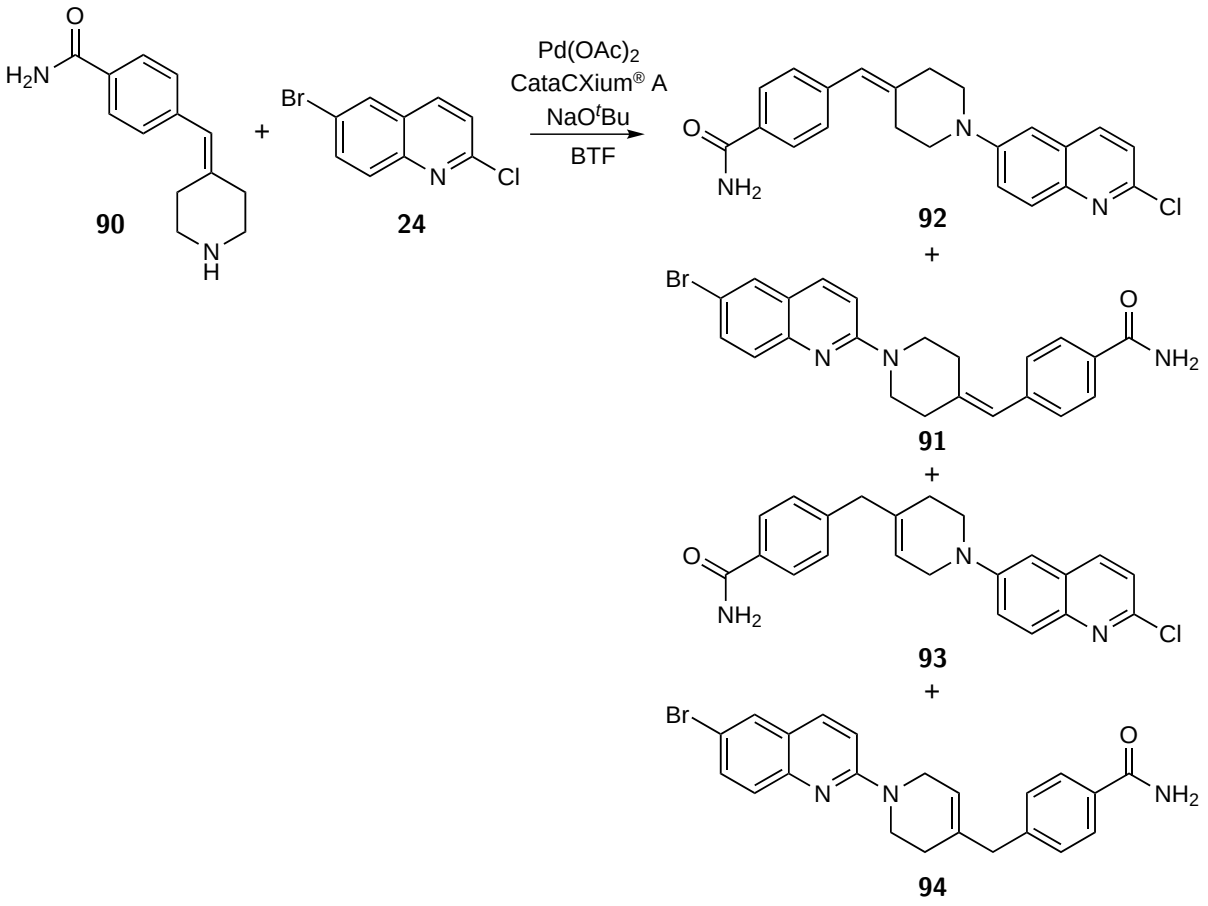


Figure 49: 2D NMR experiments used to determine substitution position for product of uncatalysed coupling reaction, **89x**. A: HMBC correlations with C_2 showing connectivity of piperidine with quinoline ring, and B: ROESY correlations showing correlations between piperidine hydrogen atoms and the quinoline ring demonstrating 2-position substitution.

Given that the only difference between the successful and unsuccessful Buchwald-Hartwig coupling reactions using the optimised conditions is the piperidine reagent, these experiments indicate that some amines may be inhibiting the activity of the palladium catalyst, and therefore preventing the selective 6-position amination reaction. It is possible that some benzyl substituents are able to coordinate to the palladium catalyst and the shape and flexibility of those piperidine derivatives enable the compounds to bind and deactivate the palladium catalyst. If this is the case, an alternate method for the synthetic process could be considered: the hydrogenation of the benzylidenepiperidine derivative (for example, reduction of **45** to give **48**) can be postponed until after the Buchwald-Hartwig aminations, thereby maintaining some rigidity in the piperidine derivative which may prevent adverse interactions with the palladium catalyst and enable the Buchwald-Hartwig amination to proceed.

This method was attempted with the Buchwald-Hartwig amination of 4-benzamide derivative **90** with **24**, but very poor conversion meant that any products could not be isolated (Scheme

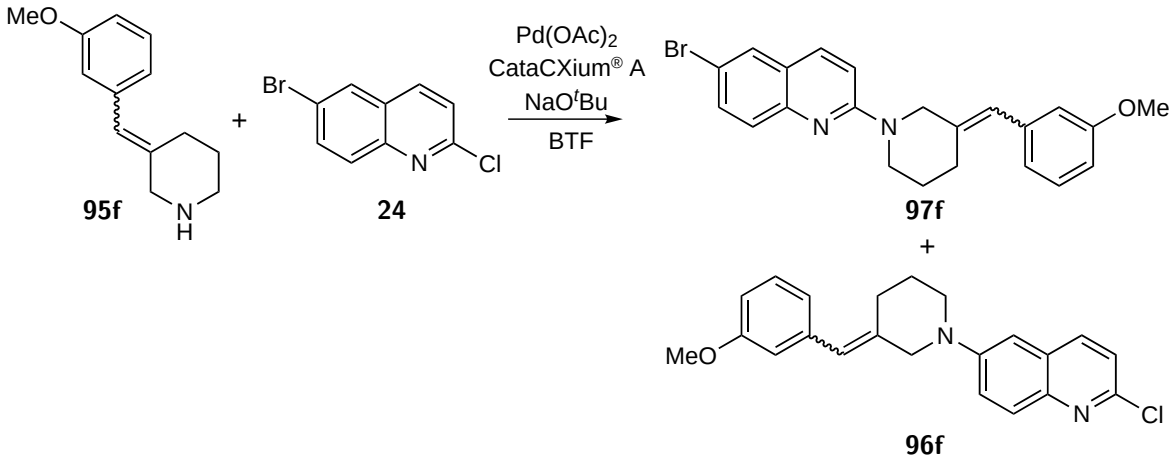
57). By inspection of the ^{1}H NMR spectra of the crude reaction mixture, it appeared the formation of 2-substituted product (**91**) had occurred although signals consistent with the desired 6-substituted product (**92**) were also observed. The characterisation of components in the reaction mixture was further complicated as the alkenes isomerise in the presence of hydroxide, and as sodium *tert*-butoxide can react with moisture to give sodium hydroxide it appears the isomerisation reaction occurred. The result of this reaction is likely each of the two isomers of the desired product (**92** and **93**) and the 2-substituted product (**91** and **94**), which could not be separated. The coupling reactions did not progress substantially with this particular amine reagent, and it was proposed that the relative hydrophilicity reduced the solubility of the amine in the non-polar BTF solvent. The same reaction was attempted using 1,4-dioxane as the solvent, and while it appeared there was better conversion to some products, the mixture of compounds present meant separation could still not be achieved.



Scheme 57: Attempted modified procedure for Buchwald-Hartwig amination of benzamide-substituted piperidine derivative **90** with **24**, with proposed major products of the reaction.

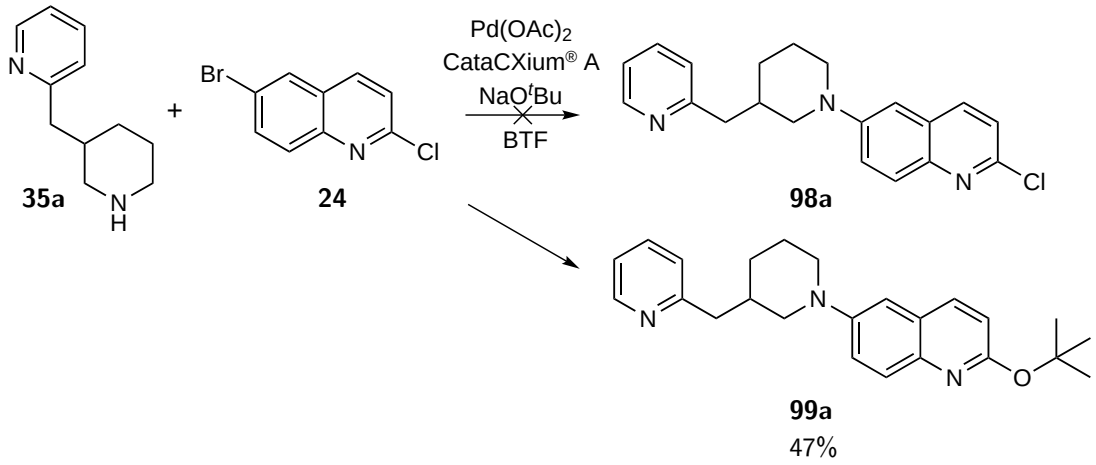
The same alternate pathway was attempted for the 3-methoxy extended 3-piperidine derivative **95f**, which was not known to isomerise in the same manner as the benzamides. In a small scale Buchwald-Hartwig reaction of **95f** with **24** a complex mixture of products was obtained and could not be purified (Scheme 58). From analysis of the crude ^{1}H NMR spectrum, signals were observed indicating that the mixture could contain both the 6-position and 2-position

coupled products (**96f** and **97f** respectively), although as *E*- and *Z*-isomers would be expected for each piperidine reagent and product the overlap of signals prevented any more accurate analysis. As signals were present consistent with the desired 6-position coupled product, the results indicate that constricting the shape of the benzylpiperidine reagent may restrict its ability to deactivate the palladium catalyst so there is more opportunity for the Buchwald-Hartwig amination to progress, at least to some extent. The low yield of this reaction meant the products could not be purified, but repeating the reaction on a larger scale, and potentially with a higher loading of palladium catalyst, may enable a workable quantity of the product to be isolated.



Scheme 58: Attempted modified procedure for coupling of 3-methoxybenzyl-extended piperidine derivative **95f** with **24** via Buchwald-Hartwig amination, which gave a mixture of products including 2-position coupled product **97f**.

The other Buchwald-Hartwig amination with atypical products was the attempted coupling of the 3-pyridinylmethylpiperidine derivative **35a** with **24**, expected to give the 6-position extended quinoline compound **98a**. Instead, the coupling reaction gave **99a**, with a 2-position *tert*-butoxy substituent, as the only product (Scheme 59). The synthesis of this compound indicates that the 6-position substitution has successfully occurred, as shown by the HMBC correlations for C_6 to piperidine hydrogen signals (Figure 50), but observation of the very distinctive *tert*-butyl signal also shows the *tert*-butoxide base has reacted further in a substitution reaction for the chlorine group at the 2-position. Under the optimised Buchwald-Hartwig reaction conditions the base is in excess (1.3 mol equiv), but typically substitution of the base at the 2-position is not observed. In the previously reported investigation of Buchwald-Hartwig conditions the 2-*tert*-butoxy product was observed under some reaction conditions tested, but typically in small yields and never reported as the only product.[52]



Scheme 59: Attempted synthesis of 3-pyridinylmethylpiperidine extended quinoline **98a** via Buchwald-Hartwig amination, which gave 2-*tert*-butoxy substituted product **99a**.

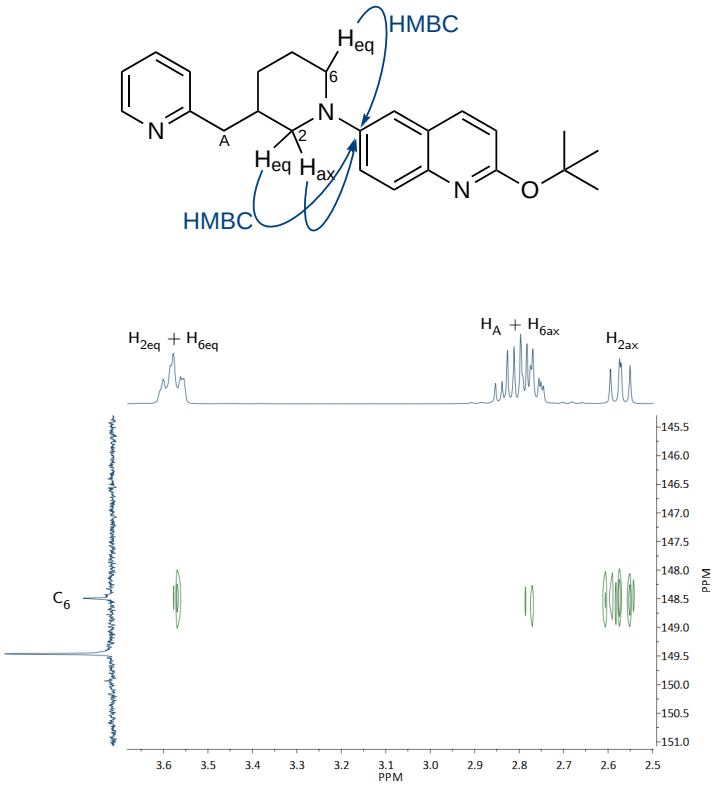
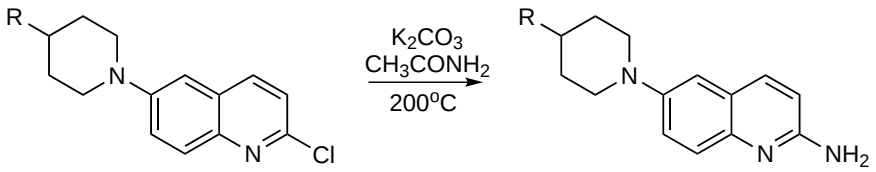


Figure 50: HMBC correlations with C_6 observed for product of Buchwald-Hartwig coupling with **35a** and **24**, showing successful coupling of piperidine at 6-position of quinoline ring.

In an attempt to reduce the formation of this undesired product, the reaction was repeated without using excess base. In this attempt only the reagents were recovered and no reaction proceeded. The reactivity of this piperidine appears to significantly differ from the other pyridine derivatives and from the other 3-benzylpiperidine derivatives, and in this work the synthesis of the target 2-chloroquinoline compound could not be achieved.

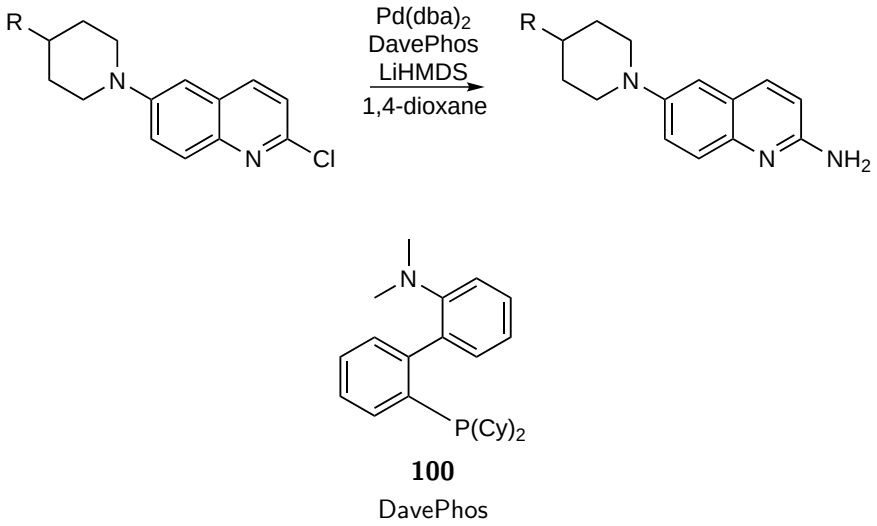
2.3.5 Synthesis of 6-position substituted 2-aminoquinolines by Buchwald-Hartwig amination

A variety of methods have been used in previous work to convert 2-chloroquinolines to 2-aminoquinolines. The Kóródi method was the most used amination procedure, however this required a very high reaction temperature and it was found to typically give low to moderate yields (4-64%, Scheme 60).[79,50,54] Another method involving 2-position substitution of a *para*-methoxybenzyl-protected amine has also been used, but while the reaction conditions are not as harsh as those required for the Kóródi method a further deprotection step is needed to yield the required amine.[54]



Scheme 60: Previously utilised Kóródi amination method for conversion of 2-chloroquinoline derivatives to corresponding 2-aminoquinolines.[52]

Most significantly, a second Buchwald-Hartwig amination was found to be an effective method used to convert several 6-position substituted 2-chloroquinolines to the corresponding 2-aminoquinolines, and higher yields of the 2-aminoquinolines could be achieved (typically 90% or greater), compared to low-moderate yields for the Kóródi method (Scheme 61).[52] The Buchwald-Hartwig amination had not been previously attempted in the synthesis of the benzylpiperidine extended ligand **15**, but given it was used very successfully to achieve amination of other 6-heterocyclic 2-chloroquinolines it was expected to work similarly with the new target derivatives.

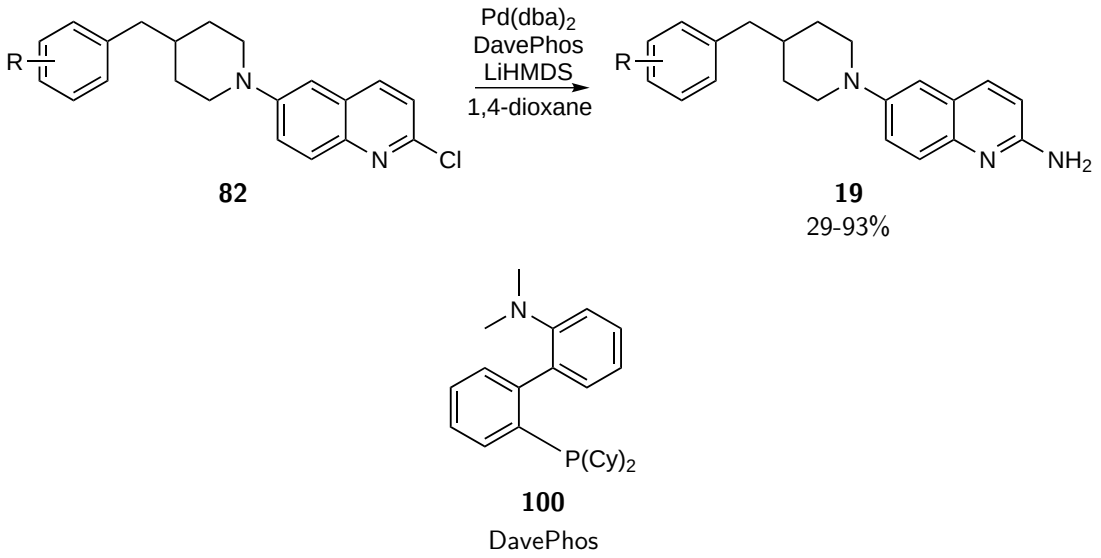


100

DavePhos

Scheme 61: Previously used Buchwald-Hartwig amination for synthesis of 6-position extended 2-aminoquinoline derivatives.[52]

These reported Buchwald-Hartwig amination conditions were applied to the conversion of 2-chloroquinoline derivatives (**82**) to the corresponding 2-aminoquinolines (**19**) using LiHMDS as both the base and ammonia source (Scheme 62). The reported catalyst system of $Pd(dba)_2$ and DavePhos (**100**) was found to be effective for all these derivatives when conducted as sealed-tube reactions in 1,4-dioxane. The reaction proceeded in all cases with typically high to complete consumption of the 2-chloroquinoline compound to give moderate to good yields of the 2-aminoquinoline ligands (Table 20).

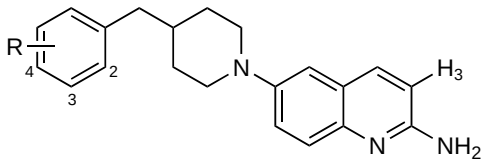


Scheme 62: General method for synthesis of target 4-benzylpiperidine extended 2-aminoquinoline derivatives (**19**) via a Buchwald-Hartwig amination reaction.

The varied results may be due to the more difficult purification of the amines by column chromatography, and also due to degradation of the product. It was observed that the isolated 2-aminoquinoline products were susceptible to some degradation over time, and this degradation was accelerated upon exposure to light. The only amendment to the previous reported method was the work-up of the reaction mixture after the sealed-tube reaction, as the previous method employed a liquid-liquid extraction which had the potential to decrease recovery of the more polar 2-aminoquinoline products if there was improved water solubility. In this work it was expected that more product could be isolated by simply quenching the mixture with methanol and filtering through Celite® before column chromatography, and therefore recovery of the more hydrophilic target compounds could be improved. The success of the 2-position amination was evident in the ^{1}H NMR and ^{13}C NMR spectra as the H_3 and C_3 signals are shielded due to the electron-donating amine substituent, and therefore shifted upfield relative to the corresponding signals for the 2-chloroquinoline precursor. Other signals in the quinoline ring which are also shielded by resonance due to the amino group were shifted upfield compared to the starting material. The presence of a broad amine hydrogen signal integrating for two hydrogen atoms was also observed for each of these products.

Likewise, for each 2-chloroquinoline derivative with a 3-benzylpiperidine or 3-benzylpyrrolidine

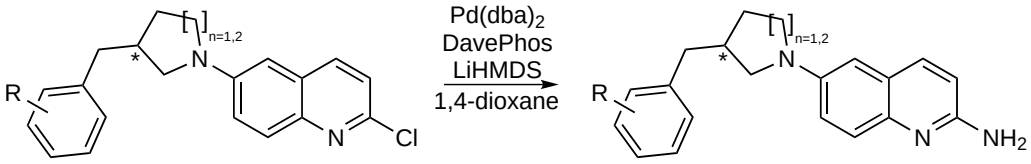
Table 20: Results of Buchwald-Hartwig amination reactions to give 6-position substituted 2-aminoquinoline derivatives with a 4-benzylpiperidine substituent (**19**) from 2-chloroquinoline derivatives (**82**).



19

	R	Yield (%)	δ_H H_3 (ppm)
19a:	4-^{t}Bu	88	6.66
19b:	2-CH_3	61	6.66
19c:	3-CH_3	46	6.67
19d:	4-CH_3	41	6.66
19e:	2-OCH_3	62	6.66
19f:	3-OCH_3	93	6.68
19g:	4-OCH_3	56	6.66
19h:	2-F	87	6.66
19i:	3-F	45	6.70
19j:	4-F	29	6.66
19n:	2-CF_3	63	6.66
19o:	3-CF_3	64	6.67
19p:	4-CF_3	33	6.67

substituent (**83** and **84** respectively) that could be synthesised in a workable quantity, the Buchwald-Hartwig amination was able to successfully yield the target 2-aminoquinoline compounds **20** (Scheme 63, Table 21). The same observations used to demonstrate success for the 4-benzylpiperidine derivatives were observed for these derivatives, particularly the upfield signals in the ^{1}H and ^{13}C NMR spectra for atoms which are comparatively shielded due to the introduction of the amino group. HRMS analysis of the products also showed loss of the chlorine substituent in each case.



n = 1: **84**
n = 2: **83**

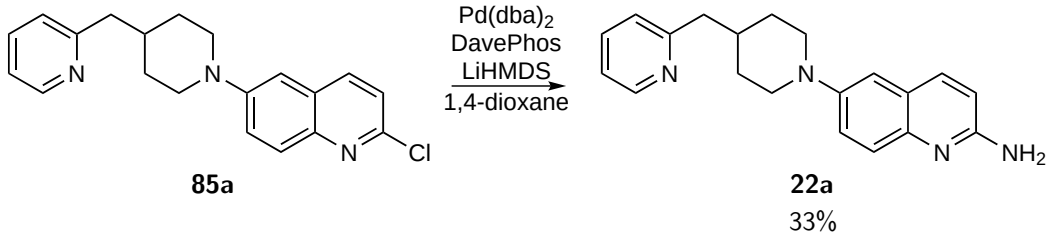
n = 1: **21x**, 70%
n = 2: **20**, 40-70%

Scheme 63: Buchwald-Hartwig amination for synthesis of 2-aminoquinoline derivatives **21** and **20** from the corresponding 2-chloroquinolines **84** and **83**. These compounds are the only 2-aminoquinoline ligands synthesised in this work that contain a stereocentre (denoted by *).

Table 21: Results of Buchwald-Hartwig aminations for synthesis of target 6-position substituted 2-aminoquinoline derivatives with a benzylpiperidine-type substituent.

	R	Yield (%)	δ_H H_3 (ppm)
3-benzylpiperidines			
20c:	3-CH_3	79	6.65
20h:	2-F	78	6.67
20j:	4-F	52	6.67
20x:	H	40	6.65
3-benzylpyrrolidines			
21x:	H	70	6.67
4-pyridinylmethylpiperidines			
22a:		53	6.67

From the 2-chloroquinoline derivatives **85a** and **85b** the corresponding 2-aminoquinolines **22a** and **22b** could be synthesised using the same Buchwald-Hartwig amination reaction conditions (Scheme 64), again with spectroscopic analysis including HRMS, ^{1}H and ^{13}C NMR, as well as 2D NMR experiments, demonstrating the successful synthesis of the target compounds.



85a **22a** 33%

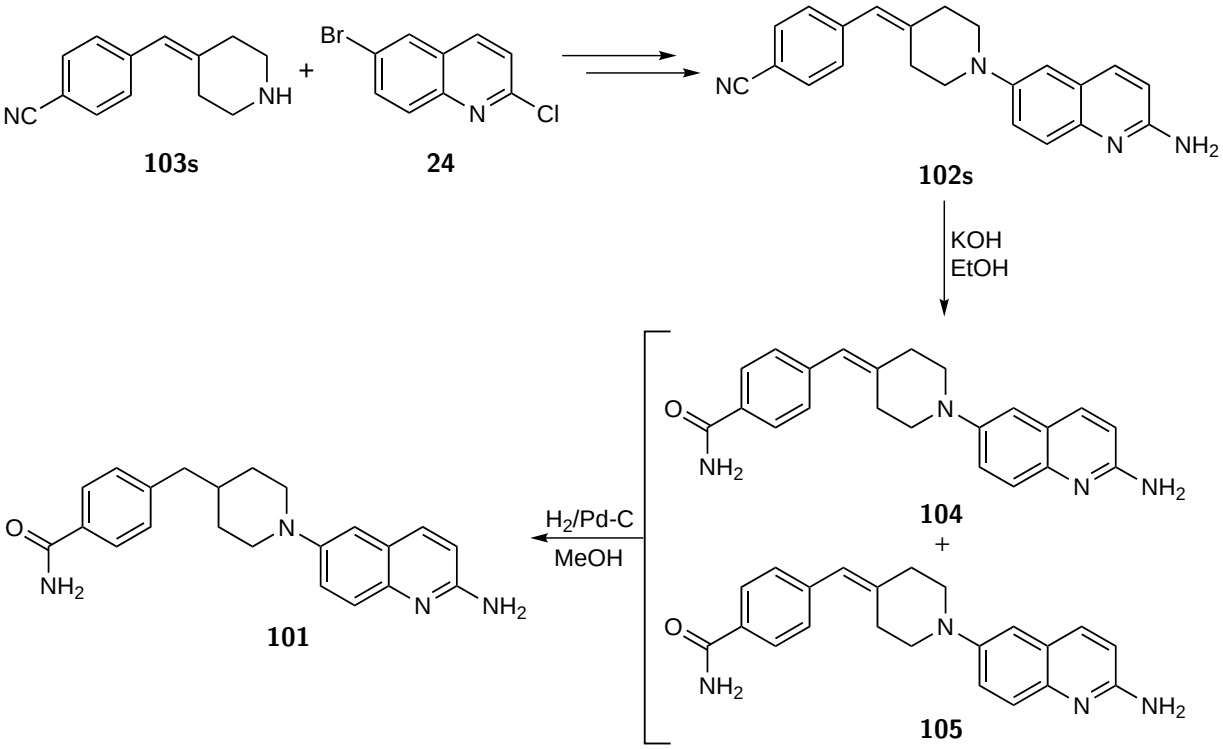
Scheme 64: Buchwald-Hartwig amination for synthesis of pyridinyl-extended 2-aminoquinoline derivative **22a**.

Alternate synthetic methods used for derivatives with atypical reactivity

The synthesis of the benzamide-subtituted 2-aminquinoline compound **101** had not yet been achieved by the previous methods, and so alternate approaches were investigated to overcome the non-selective Buchwald-Hartwig coupling of **24** and the benzamide reagents (see Schemes 54 and 57). It was difficult to identify the products formed under Buchwald-Hartwig amination conditions as the reaction progressed very slowly and therefore yielded very little product, and the spectra of the crude reaction mixtures of the alkenes were significantly complicated due to the isomerisation of benzylidenepiperidines to tetrahydropyridines (see Figure 42).

As solubility was expected to be causing the issues with low reactivity under Buchwald-Hartwig amination conditions, an alternate strategy via synthesis and then hydrolysis of the benzonitrile-extended target compound **102s** would potentially resolve the poor solubility and

conversion issues (Scheme 65). This pathway would require the hydrogenation to occur as the final step after the hydrolysis, otherwise partial reduction of the nitrile bond would be expected to reduce the yield and complicate purification. It would be anticipated that the hydrolysis would cause the isomerisation to occur and give both the piperidine and the tetrahydropyridine products, however subsequent hydrogenation of the mixture of products would be expected to yield the single product, compound **101**.



Scheme 65: Proposed alternate synthetic pathway for benzamide-substituted 2-aminoquinoline ligand **101**.

Leaving the hydrogenation until after the Buchwald-Hartwig aminations to make the 2-aminoquinoline structure had not been attempted previously, and therefore the synthesis of the simpler derivative, **15**, via the aminoquinoline **102x** was first attempted as a test to investigate whether this reaction would occur. The proposed synthesis of **102x** was again via a Horner-Emmons reaction to make the Boc-protected benzylidenepiperidine **45x**, which would be followed by deprotection of the Boc-protecting group to give the piperidine **103x** (Figure 51). The successive Buchwald-Hartwig aminations would then give the 2-aminoquinoline compound **102x**, following which hydrogenation could be attempted to give the target 2-aminoquinoline **15**.

The synthesis of **45x** was achieved via Horner-Emmons reaction of **36x** and **44** (Scheme 66). The reaction proceeded with moderate yield and results comparable to those obtained for other derivatives of **45** previously (see Table 6). Spectroscopic data, including HRMS and NMR experiments, confirmed the successful synthesis of the desired structure. The

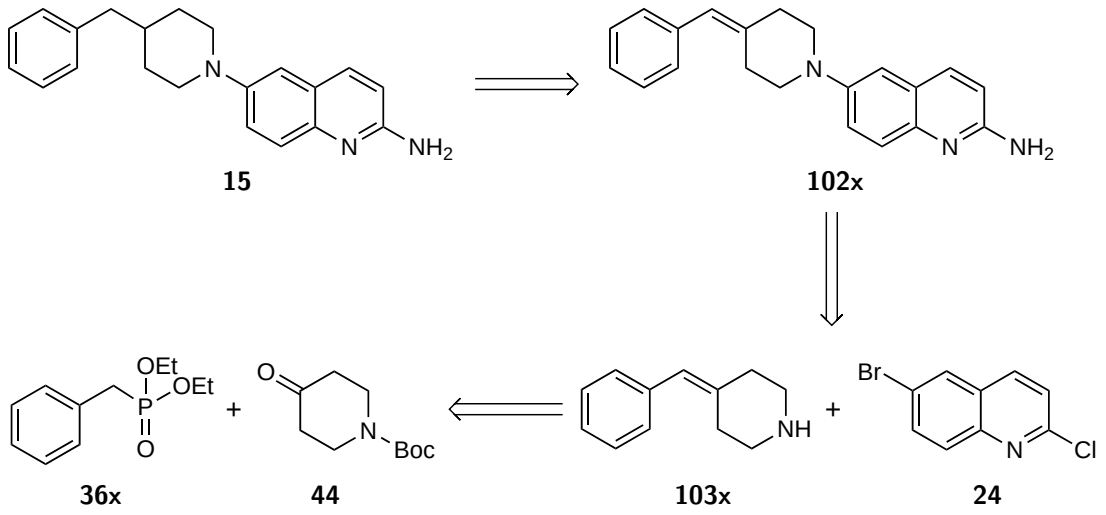
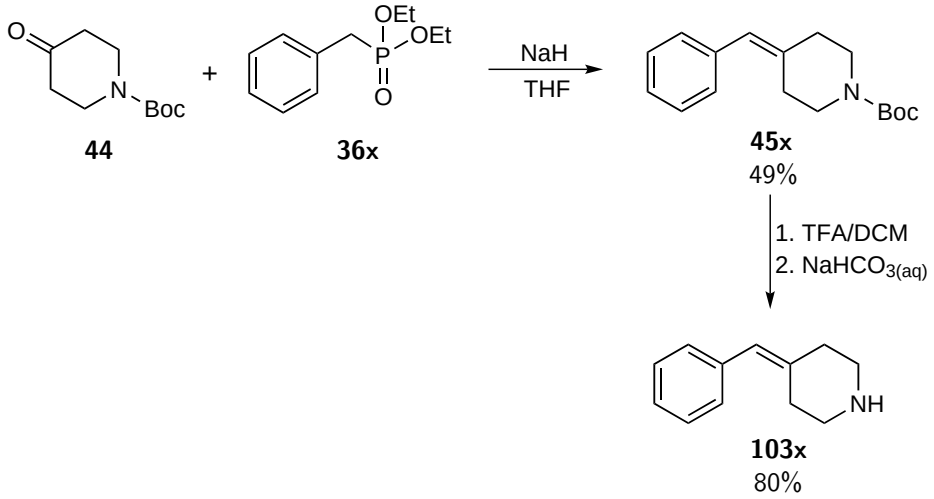


Figure 51: Proposed retrosynthesis of **15** via 4-benzylidenepiperidine extended 2-aminoquinoline **102x**.

^{1}H NMR spectrum showed the key singlet signal corresponding to the alkene hydrogen at 6.36 ppm, and broad signals consistent with the substantially planarised piperidine ring structure as previously described for other Boc-protected piperidines.

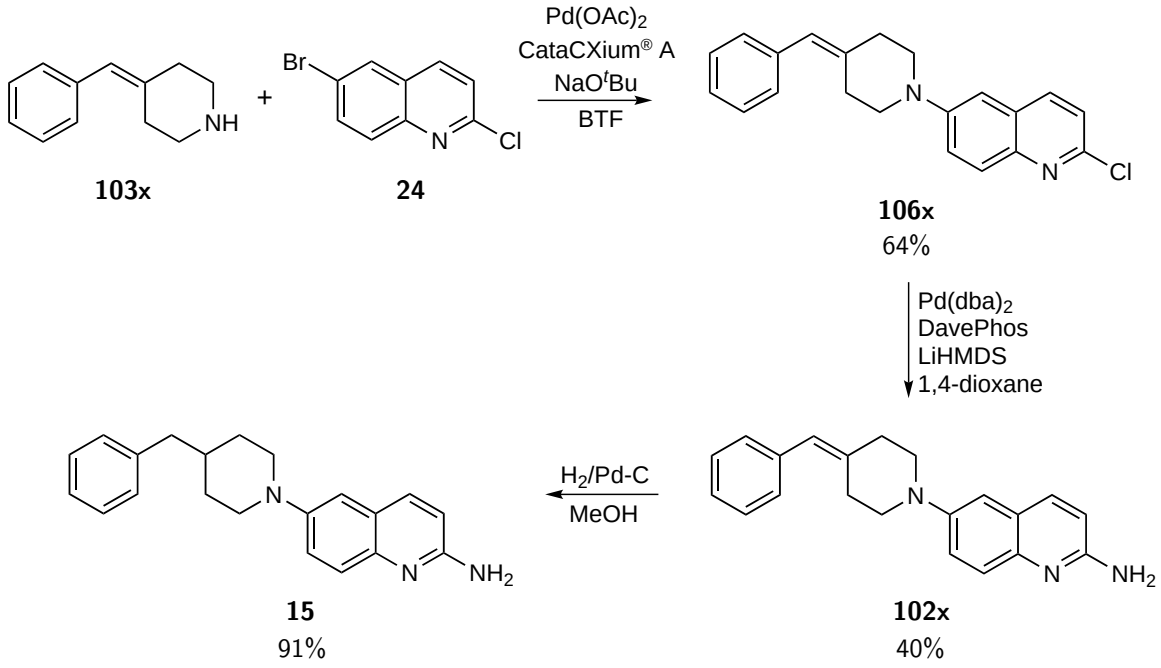


Scheme 66: Synthesis of 4-benzylidenepiperidine (**103x**) via Horner-Emmons reaction pathway.

The Boc-protecting group was then removed using the TFA-catalysed deprotection method, with high yield of the free amine product **103x** obtained. The spectroscopic results for the product were consistent with loss of the Boc-protecting group while the alkene was retained. The NMR spectra of the product indicate the piperidine ring retained a similar conformation to the precursor, instead of a more chair-like conformation, as each methylene group of the piperidine ring corresponds to one signal in the ^{1}H NMR spectrum instead of giving a more complex pattern of distinct axial and equatorial signals.

4-Benzylidenepiperidine (**103x**) was then reacted with **24** under the Buchwald-Hartwig amination conditions used to make the 2-chloroquinoline derivatives previously, with moderate yield of **106x** achieved (Scheme 67). 2D NMR experiments were used to confirm that the

piperidine coupled successfully at the 6-position of the quinoline ring, and no other products were isolated or observed in the crude ^{1}H NMR spectrum. HRMS was also used to confirm that the 2-position chloro-substituent was present in the product.



Scheme 67: Synthesis of benzylidenepiperidine- and benzylpiperidine-extended 2-aminoquinoline derivatives from **103x** via Buchwald-Hartwig aminations.

The 2-aminoquinoline product **102x** was then synthesised from **106x** by Buchwald-Hartwig amination using LiHMDS, with the successful reaction demonstrated using spectroscopic techniques including HRMS and distinctive shifts in the NMR spectra as described for synthesis of other 2-aminoquinoline derivatives previously, most distinctively by the upfield shift of the H_3 signal of the quinoline ring compared to the reagent **106x**, due to the electron-withdrawing amino substituent. The shape of the piperidine ring could be deduced from the spectroscopic results, as the HSQC experiment showed correlations between each piperidine ring carbon signal and one broad 2H ^{1}H NMR signal which indicates a substantially planarised ring, instead of correlations with distinct axial and equatorial signals which would be observed for a more chair-like ring conformation (Figure 52A). ROESY correlations were used to assign the hydrogen signals for each methylene group of the asymmetric piperidine ring, and the ROESY correlations observed between the piperidine signals and the quinoline ring signals demonstrated the 6-position substituted quinoline structure (Figure 52B).

The final and key step was hydrogenation of **102x**, and using standard hydrogenation conditions it was found that the target **15** could be effectively achieved from **102x** in high yield, with the corresponding increase in mass found by HRMS analysis. The spectroscopic results were consistent with the change in structure as previously reported,[52] with loss of the alkene hydrogen signal in the ^{1}H NMR spectrum and an additional 2H signal corresponding to the methylene hydrogen atoms of the benzyl group, which appeared as a doublet. The change

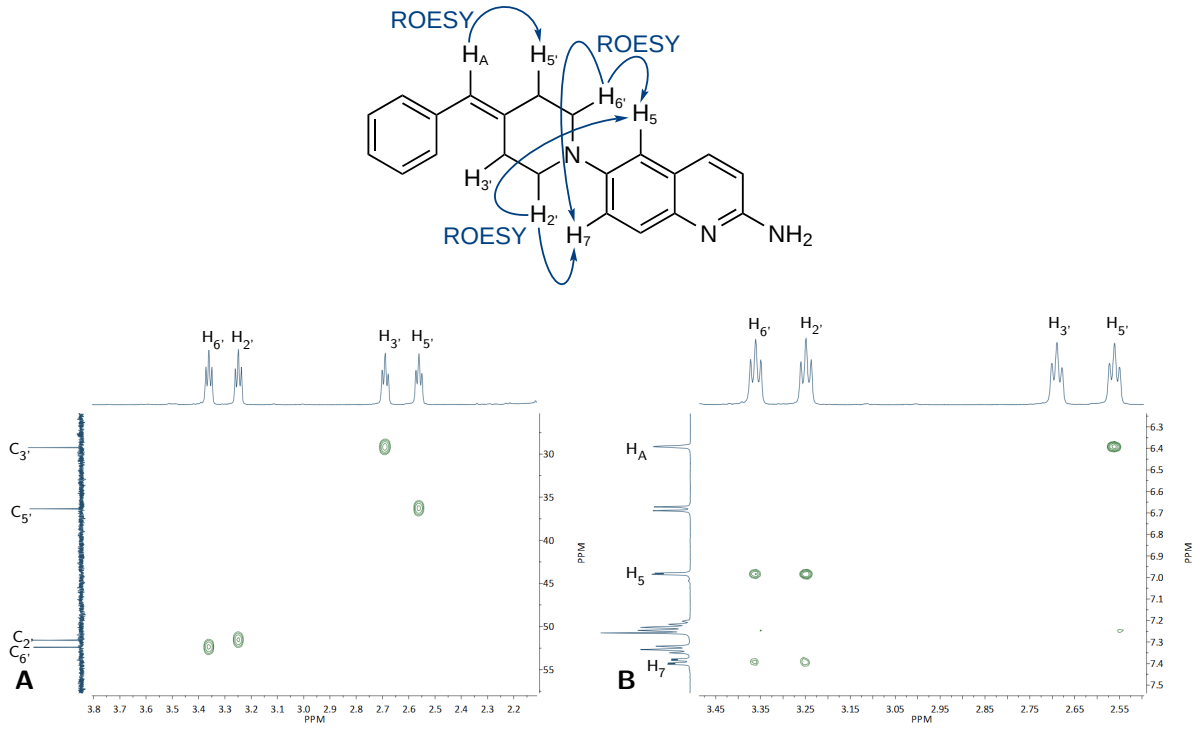


Figure 52: 2D NMR experiments used to assign signals of benzylidene-substituted ligand **102x**, and demonstrating shape of piperidine ring. A: HSQC correlations of methylene signals for substantially planarised piperidine ring, and B: ROESY correlations demonstrating quinoline substitution position and assignment of inequivalent methylene hydrogen signals .

in piperidine ring conformation compared to the alkene precursor is also evident due to the distinct axial and equatorial hydrogen signals observed, and characteristic coupling constants measured for those signals which were consistent with geminal and axial-axial coupling for a chair-like piperidine ring conformation (Figure 53).

Following the successful synthesis of **15** via **102x**, the similar but more ambitious synthesis of **101** was attempted. A high yield of pure **45s** had been achieved via Horner-Emmons reaction using LiHMDS as the base as described previously, and this product was treated with TFA under standard Boc-deprotection conditions to give the desired product **103s** with a high yield (Scheme 68). The removal of the Boc-protecting group was clearly demonstrated by the lack of large *t*-butyl signals in the NMR spectra, and an upfield shift for the piperidine hydrogen signals adjacent to the piperidine nitrogen in the ^{1}H NMR spectrum due to loss of the anisotropically deshielding carbonyl group. The similarities in the spectroscopic data compared to **103x** supported the analysis that the desired benzylidenepiperidine product was obtained and none of the tetrahydropyridine product was observed.

The product **103s** was then coupled with **24** in a Buchwald-Hartwig amination under the established standard reaction conditions as a sealed tube reaction in BTF. The reaction yielded a crude mixture which was found by ^{1}H NMR analysis to contain the desired product **106s** and the undesired 2-position coupled product **107s**, as well as recovered reagents (Scheme 68).

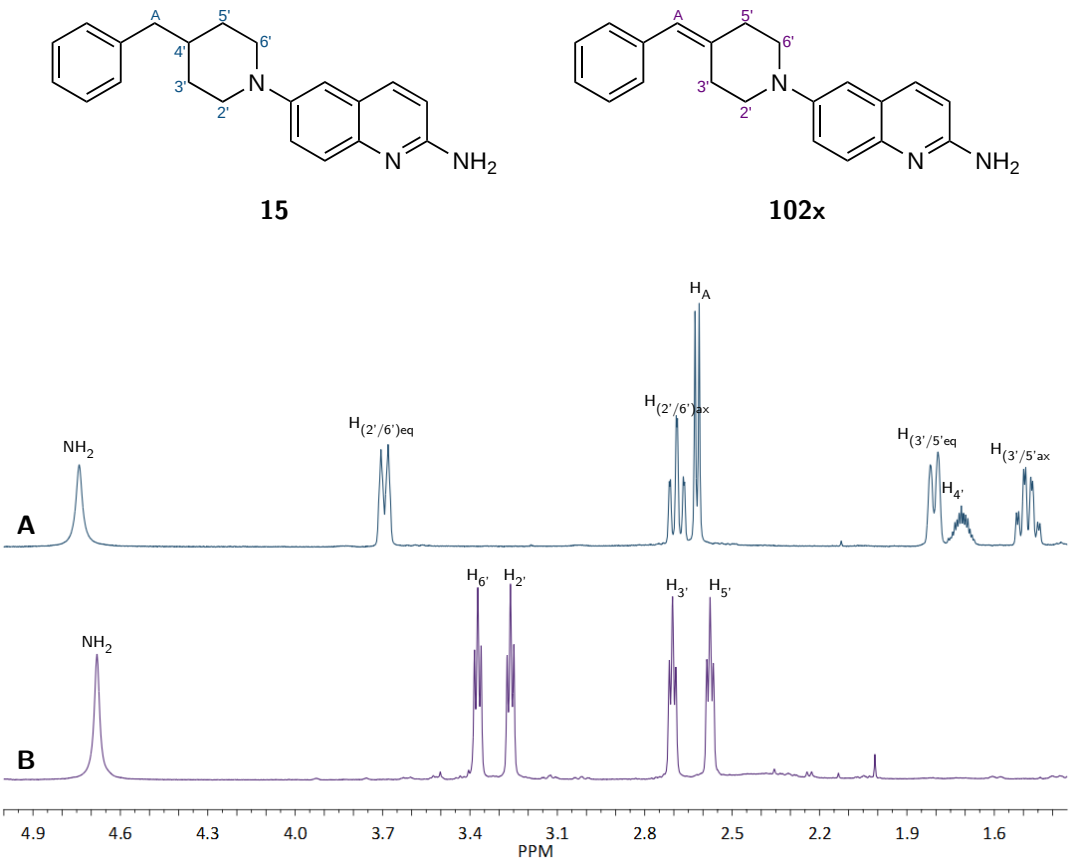
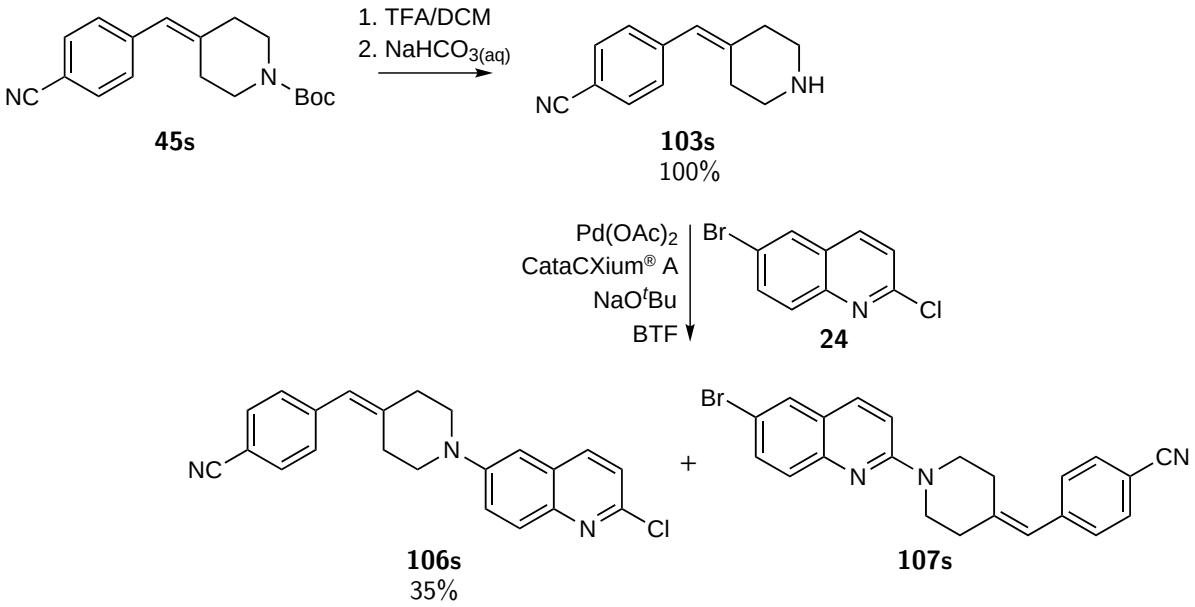


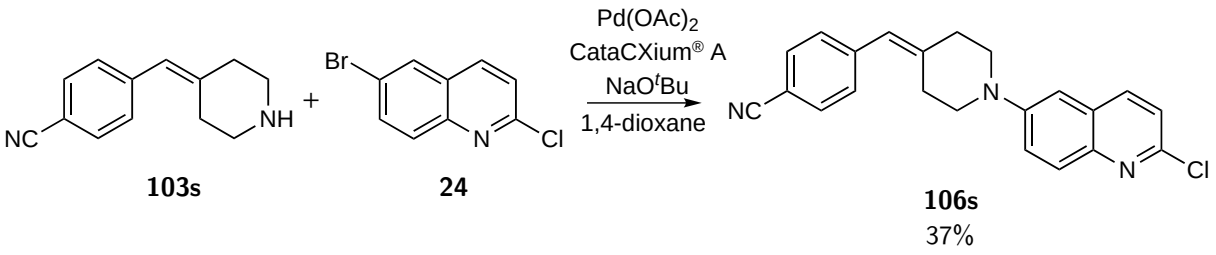
Figure 53: Comparison of ^{1}H NMR spectra of 2-aminoquinoline ligands. A: Benzylpiperidine-substituted 2-aminoquinoline **15**, and B: benzylidenepiperidine-substituted 2-aminoquinoline **102x**.



Scheme 68: Attempted synthesis of benzonitrile-extended 2-chloroquinoline **106s** via Buchwald-Hartwig coupling reaction of **24** and **103s** in BTF. Side-product **107s** could not be isolated.

A low yield (35%) of the desired product was isolated, however a large amount of recovered reagents was also obtained. The low conversion indicated that the reagents, specifically

the benzonitrile compound **103s**, may not be sufficiently soluble in the relatively non-polar solvent, and therefore the same reaction was attempted using 1,4-dioxane as the reaction solvent (Scheme 69).



103s + **24** → **106s** 37%

Scheme 69: Synthesis of benzonitrile-extended 2-chloroquinoline derivative **106s** via Buchwald-Hartwig coupling reaction of **24** and **103s** in 1,4-dioxane.

A slightly higher yield of the desired 6-position coupled product **106s** was isolated from the attempted Buchwald-Hartwig amination in 1,4-dioxane, and none of the 2-position coupled product was observed in the crude mixture. The success of the reaction was confirmed by HRMS of the isolated product which was consistent with the 2-chloroquinoline product instead of a bromo-substituted product, and by analysis of the NMR spectra. The ^{1}H NMR signals for the quinoline ring were consistent with 6-position extended 2-chloroquinolines isolated previously. The distinct dd signal for H_7 and the doublet signal for H_5 were shifted upfield for the 6-position substituted product **106s**, in contrast the 2-position coupled product (**107s**) where the H_3 signal is shifted further upfield due to the effect of the electron-donating piperidine substituent. In addition, the 2D ROESY NMR experiment showed correlations between the H_5 and H_7 signals and the piperidine hydrogen atoms adjacent to the nitrogen atom for the 6-position coupled product only. The signals for the piperidine ring appeared as broad 2H signals correponding to each methylene in the ring, and the 2D ROESY NMR experiment was used to determine which signals were closest to the benzonitrile (Figure 54).

These results indicate that the change to a more polar solvent may be preferable for piperidine reagents which demonstrate poor conversion or poor selectivity under Buchwald-Hartwig conditions in BTF. In contrast, the synthesis of the simpler 4-benzylpiperidine-extended compound **82x** had been attempted using 1,4-dioxane as the solvent, and was found to yield a much more complicated mixture of products. Identified products from that reaction included a substantial amount of the 2-position coupled quinoline product **27x** and the products could not be separated by chromatography showing the change of solvent is not always favourable for formation of the desired 2-chloroquinoline product (Scheme 70) .

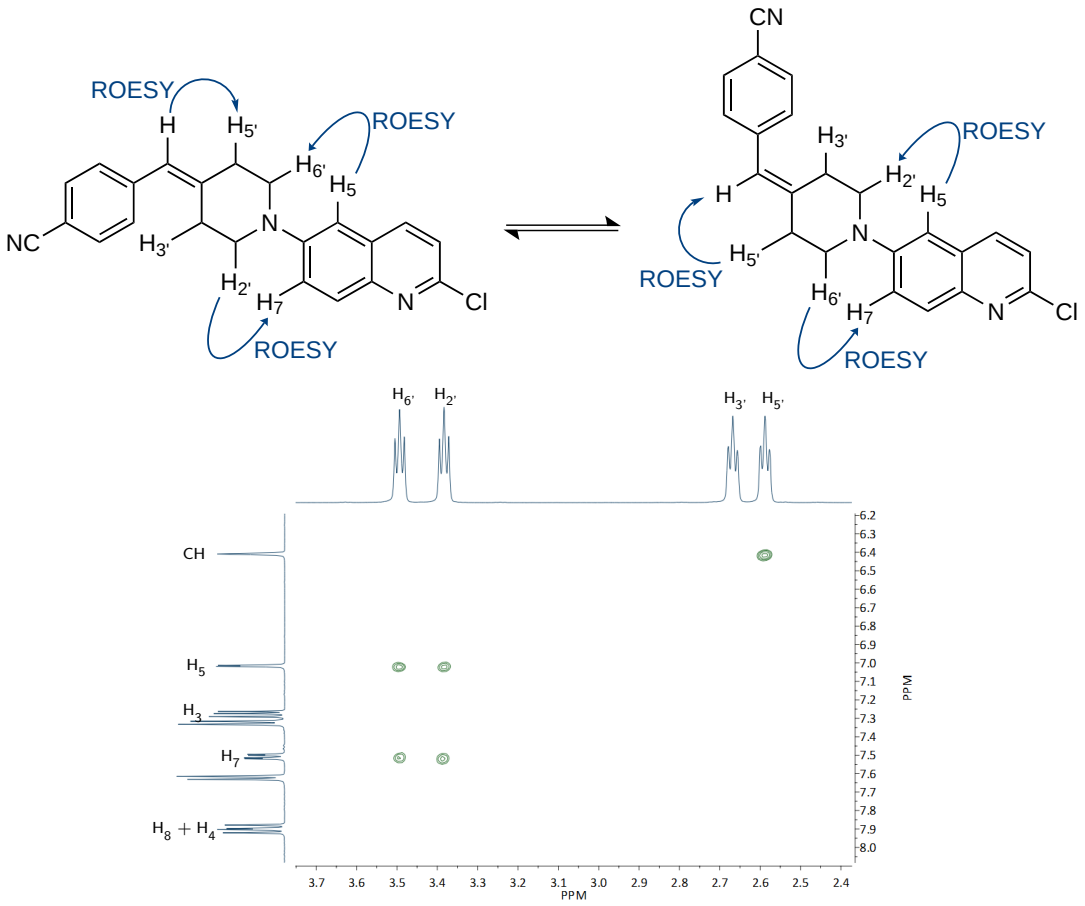
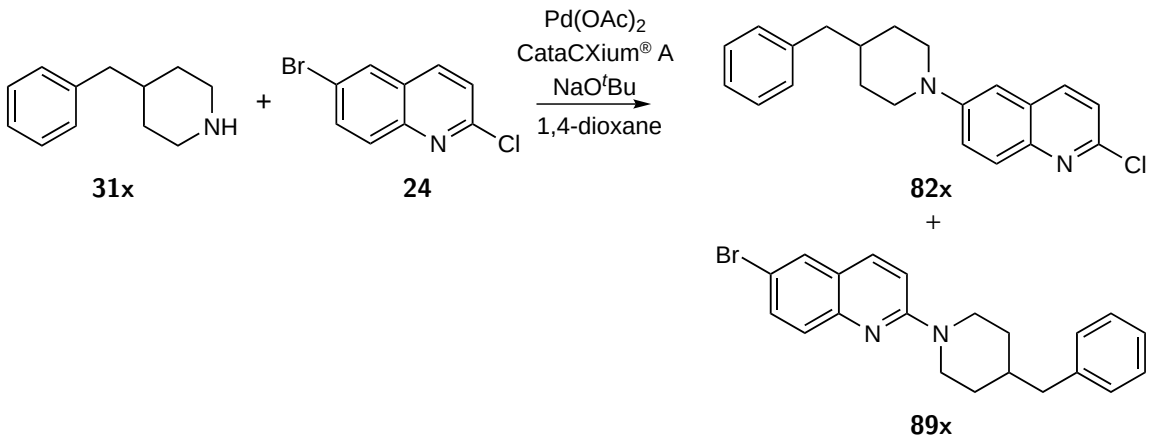


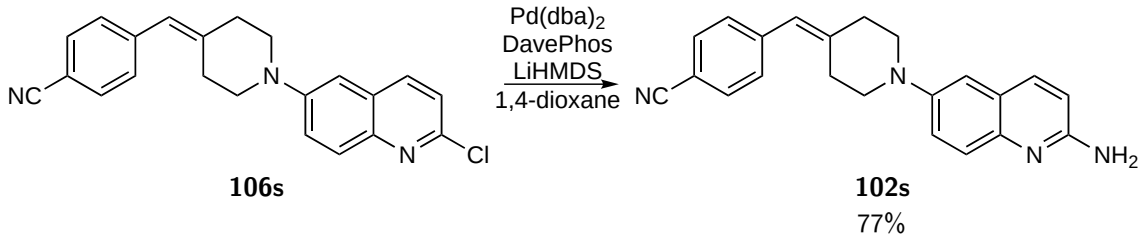
Figure 54: ROESY correlations between piperidine ring and quinoline ring, demonstrating successful synthesis of 6-position substituted 2-chloroquinoline **106s**.



Scheme 70: Attempted coupling reaction of 4-benzylpiperidine (**31x**) and 6-bromo-2-chloroquinoline (**24**) under Buchwald-Hartwig conditions with 1,4-dioxane. Reaction gave a mixture of products which could not be separated. By crude ^{1}H NMR analysis and comparison to pure compounds isolated previously, approximate ratio of products **82x** and **89x** was 6:1 (c.f. Table 18, Scheme 56).

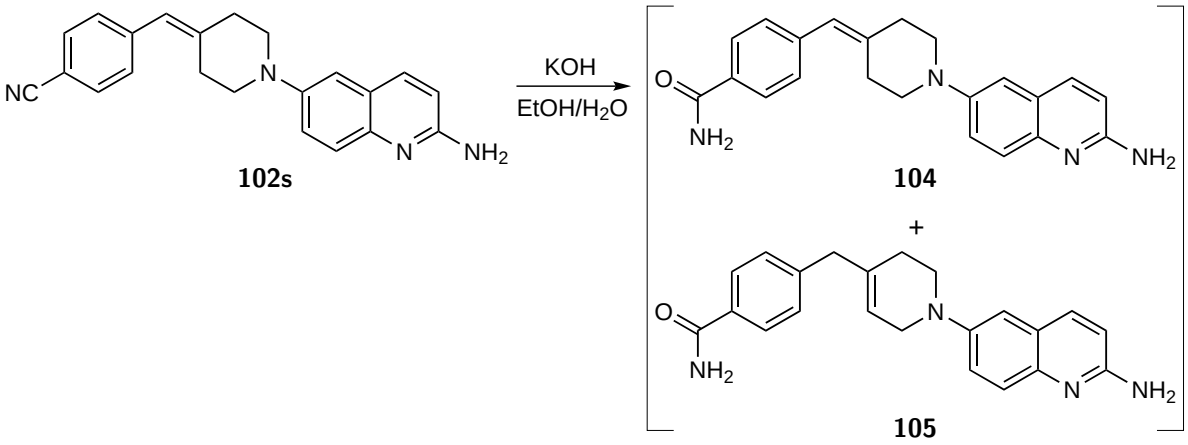
The 2-chloroquinoline compound **106s** was converted to the 2-aminoquinoline compound **102s** under the standard amination conditions with LiHMDS as the base and amine source (Scheme 71). This reaction proceeded effectively, with success indicated by the upfield H_3 shift in the ^{1}H NMR spectrum, and the change in mass corresponding to loss of the chloride

and introduction of the amino group determined by HRMS analysis, as observed for all 2-aminoquinoline derivatives synthesised previously.



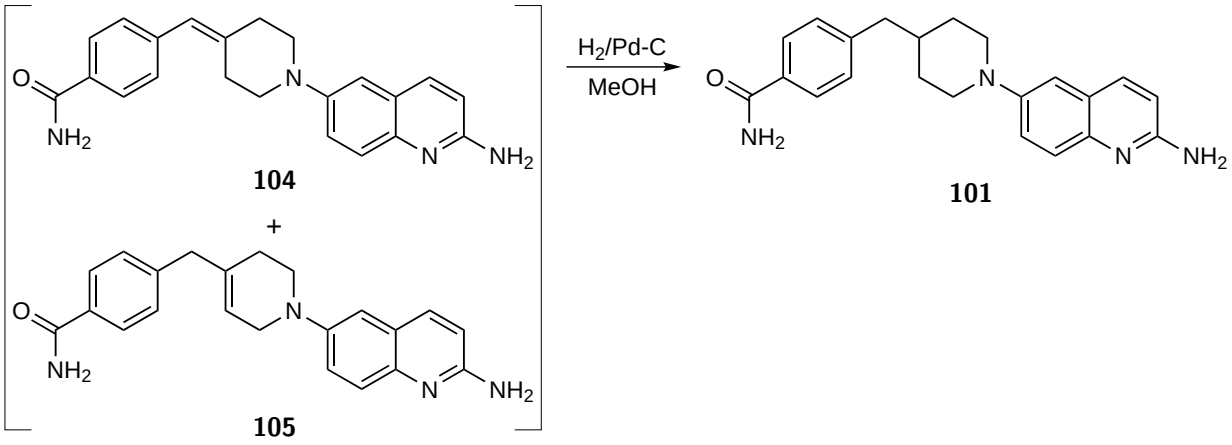
Scheme 71: Buchwald-Hartwig amination of benzonitrile extended 2-chloroquinoline derivative **106s** to give 2-aminoquinoline product **102s**.

Hydrogenation at this point would be expected to partially reduce the nitrile bond, as was indicated by the results of hydrogenation of **45s** previously, and so the conversion of the nitrile group to the amide by hydrolysis was the preferable next step in the synthetic pathway. This was achieved by hydrolysis using potassium hydroxide in ethanol, similar to those used to synthesise the benzamide **59** previously (Scheme 72). The hydrolysis reaction did not proceed under gentle reaction conditions at room temperature, and therefore the reaction progress was heated at reflux and carefully monitored by TLC in order to minimise further hydrolysis of the desired amide product. When the reaction was complete the amide product was extracted from the reaction mixture and purified by column chromatography. Interpretation of the NMR data for the product was difficult as both alkene isomers of the product were present, however HRMS was used to show the desired mass peak for the product **104** (and therefore its structural isomer **105**) was present indicating the success of the hydrolysis reaction.



Scheme 72: Hydrolysis of benzonitrile-extended 2-aminoquinoline **102s** to give inseparable mixture of benzamide isomer products **104** and **105**.

As the final step in the synthesis, the mixture of alkene structural isomers was reacted under hydrogenation conditions for 24 hours - the extended reaction time is due to the less accessible alkene in the tetrahydropyridine product **105**, which takes longer to reduce to the desired product under the same reaction conditions (Scheme 73).

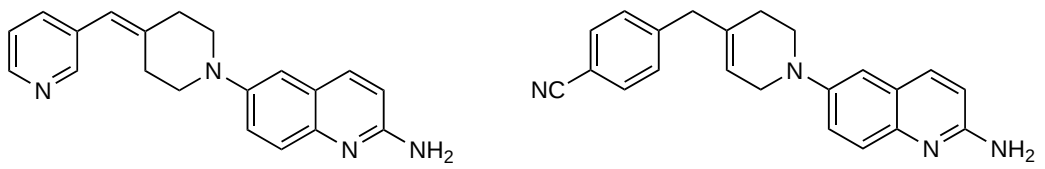


Scheme 73: Hydrogenation of inseparable mixture of benzamide-extended 2-aminoquinolines **104** and **105** to give final ligand compound **101**.

HRMS analysis was used to confirm an increase in the mass corresponding to two hydrogen atoms, consistent with the desired product. NMR spectroscopy was used to determine that only one product was present as the result of the hydrogenation of both alkenes to give **101** as desired. The appearance of the signals in the ^{1}H NMR spectrum of the product was highly similar to the other substituted benzylpiperidine derivatives. Axial and equatorial signals with characteristic coupling constants were observed for each piperidine ring signal, and the comparatively upfield signals observed for the H_3 and H_5 quinoline ring hydrogen atoms are indicative of the electron-donating amine substituents attached at the 2- and 6-positions of the quinoline ring, consistent with the target structure. Broad NH signals were observed for the 2-position amino substituent on the quinoline ring and for the amide substituent on the benzylpiperidine group. Combined, the spectroscopic data strongly supports successful synthesis of the benzamide target **101** by this alternate synthetic pathway.

From the successful synthesis of these 2-aminoquinoline derivatives with benzylidenepiperidine-type substituents, other similar desired products were also proposed. Given only one pyridinylmethylpiperidine derivative (**22a**) had been synthesised via the general method previously, it was proposed that instead of the low yielding synthetic pathway of the 3-pyridine derivative **22b** the analogous compound **108b** could instead be a useful target (Figure 55). The benzylidene substituent results in a substantially planarised piperidine ring, and therefore may have an effect upon the strength of the binding interaction with the Tec SH3 domain and therefore give some information on the shape of the ligand required to optimally bind to this protein target.

Also, to further investigate the impact of different 3-dimensional shapes of the piperidine substituent upon binding to the Tec SH3 domain, the tetrahydropyridine-extended compound **109s** was also a proposed target compound. From the related compounds made previously, interpretation of the NMR data for the tetrahydropyridine products suggested that these

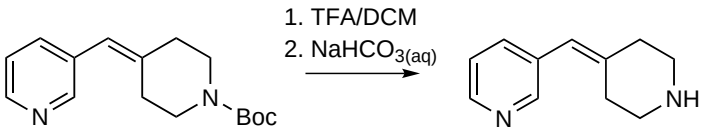


108b **109s**

Figure 55: Further proposed 2-aminoquinoline target compounds with more planarised alkene substituents.

compounds have a substantially planarised ring conformation, likely similar to the benzylidenepiperidine compounds, however the benzyl group is freely rotating and therefore may make more similar contacts with the protein target that were achieved with the benzylpiperidine lead compound.

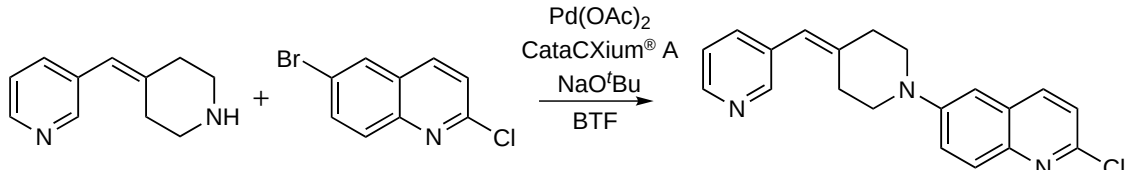
Firstly, for the synthesis of **108b**, the alkene precursor **53b** had been prepared via a Wittig reaction previously. This compound was treated with TFA to remove the Boc-protecting group (Scheme 74). A low yield of product **110b** was achieved, which was again proposed to be due to the higher water solubility of the pyridine product compared to benzyl-substituted piperidines, but in this case a sufficient quantity was achieved to enable continuation of the synthetic pathway.



53b **110b**
20%

Scheme 74: Synthesis of pyridinylmethylidenepiperidine derivative **110b** via Boc-deprotection of **53b** with TFA.

The compound **110b** was then coupled with the quinoline **24** using the established Buchwald-Hartwig amination procedure, and a moderate yield of the desired 6-position substituted 2-chloroquinoline product **111b** was obtained (Scheme 75).



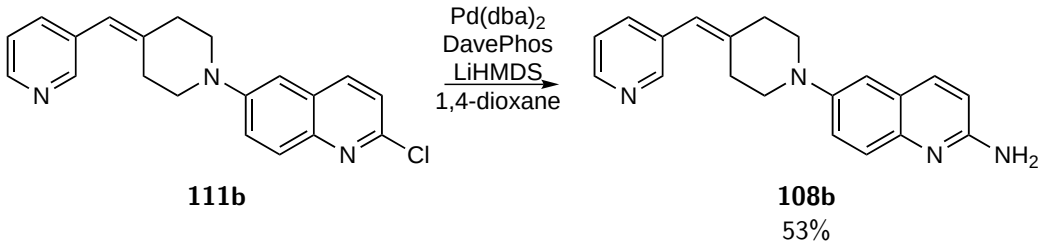
110b **24** **111b**
46%

Scheme 75: Synthesis of pyridinyl-extended 2-chloroquinoline derivative **111b** via Buchwald-Hartwig coupling reaction of **24** and **110b** in BTF.

Importantly, none of the undesired 2-position coupled product was observed after work-up of the reaction, and the only isolated product was clearly demonstrated by spectroscopic analysis to be 6-position couple product. HRMS analysis showed peaks consistent with the

chloroquinoline product, and the characteristic upfield chemical shifts of the H_5 and H_7 signals were observed in the ^{1}H NMR spectrum as expected.

The final step of the synthesis of the target compound was the second Buchwald-Hartwig amination with LiHMDS, and this yielded the target compound **108b** (Scheme 76). The upfield shift of the H_3 signal in the ^{1}H NMR spectrum and the decrease in the HRMS mass peak found were used to confirm the success of the amination reaction. In contrast to the pyridinylmethylpiperidine ligand **22a** made previously, the ^{1}H NMR spectrum did not give a series of signals consistent with a chair-like piperidine ring conformation. Instead, the signals indicated a substantially planarised ring as expected for this type of structure, with the broader ^{1}H NMR signals corresponding to each of the methylene groups. 2D NMR experiments, including ROESY, were used to definitively assign each of the signals to each methylene group, similarly to analogous compounds described previously.

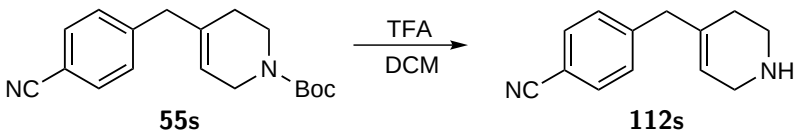


111b **108b** 53%

Scheme 76: Buchwald-Hartwig amination of pyridinyl-extended 2-chloroquinoline derivative **111b** to give the corresponding 2-aminoquinoline product **108b**.

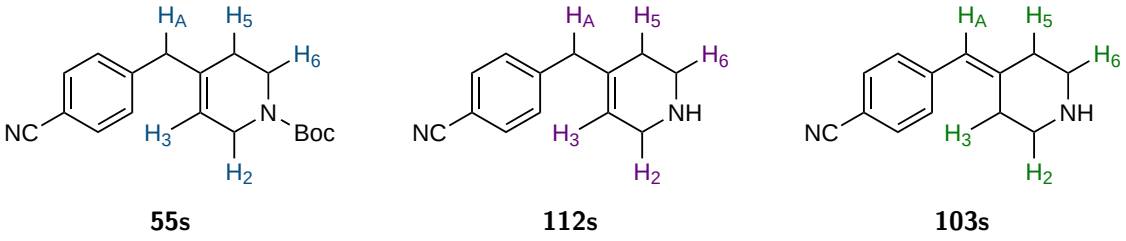
The other target ligand, the tetrahydropyridine compound **109s**, could not be effectively synthesised in the same way. Tetrahydropyridines are notoriously difficult to synthesise selectively, and therefore the method serendipitously discovered in this work was deemed the most simple method to obtain a tetrahydropyridine compound even though it is not selective. Using that method, a Horner-Emmons reaction of the Boc-protected piperidone **44** with **36s** gave a mixture of **45s** and **55s** as described previously, and repeated column chromatography gave a reasonable yield of pure **55s** which could be used in the subsequent synthesis.

The sample of **55s** was then treated with TFA to remove the Boc-protecting group (Scheme 77). This gave a crude oil which was purified by column chromatography to give one major product. The NMR data clearly showed the loss of the signals corresponding to the Boc-protecting group, and the HRMS data was consistent with the desired product. There were clear similarities between the signals of the obtained product and the tetrahydropyridine reagent, and these observations were used with 2D NMR methods to determine that the major product was definitively the desired tetrahydropyridine **112s** (Figure 56). The most apparent similarity was the broad alkene signal at 5.44 ppm in the ^{1}H NMR spectrum, which appears upfield compared to the alkene signal for the benzylidenepiperidine isomer **103s** (6.32 ppm) and at a very similar shift to the tetrahydropyridine precursor **55s** (5.38 ppm).



55s **112s**

Scheme 77: Synthesis of tetrahydropyridine compound **112s** via Boc-deprotection of **55s** with TFA.



55s **112s** **103s**

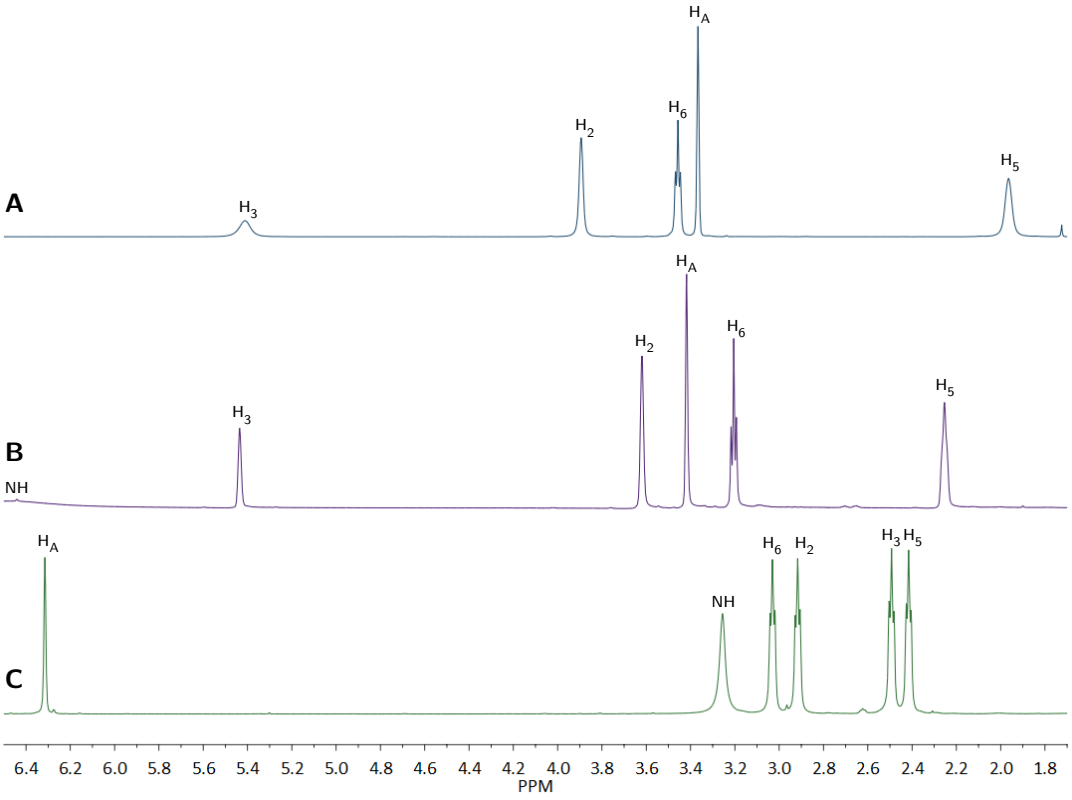
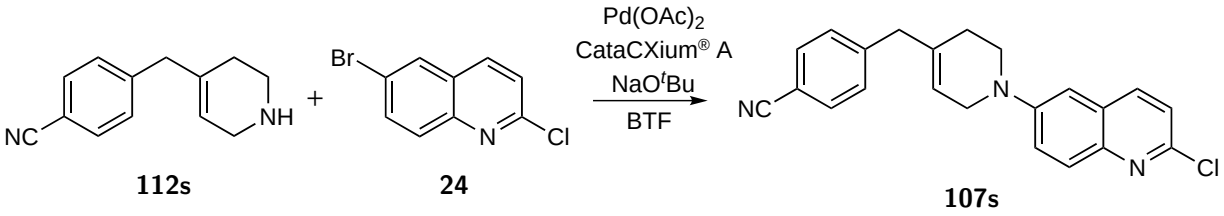


Figure 56: Comparison of ^{1}H NMR spectra for alkene compounds, indicating the distinct 3D structures of the benzylidene and tetrahydropyridine compounds. A: Boc-protected tetrahydropyridine reagent **55s**, B: product of deprotection reaction **112s**, C: benzylidenepiperidine isomer **103s**.

The Buchwald-Hartwig coupling of **112s** with **24** in BTF was achieved using the general method previously utilised in this work, and the desired 6-position coupled product **107s** was obtained (Scheme 78). HRMS analysis of the isolated product confirmed that the mass peaks were consistent with the chloro-substituted product, and none of the 2-position coupled 6-bromoquinoline side-product was observed in this case. The structure of the Buchwald-Hartwig product was studied by analysis of the NMR spectra. Under the Buchwald-Hartwig reaction conditions, isomerisation of the product **107s** to **106s** was not observed in the NMR

spectra, and instead key spectroscopic characteristics of only the tetrahydropyridine compound were observed. Clear signals confirming successful coupling of the tetrahydropyridine to the 6-position of the quinoline reagent were distinct in the ^{1}H NMR spectrum of the product, specifically the upfield chemical shifts of the distinctive H_5 doublet signal ($^4J_{5,7} = 2.7$ Hz) and the H_7 doublet of doublets signal ($^3J_{7,8} = 9.3$ Hz, $^4J_{5,7} = 2.7$ Hz) compared to the quinoline reagent, to 6.97 ppm and 7.49 ppm respectively.



Scheme 78: Synthesis of benzonitrile-extended 2-chloroquinoline derivative **107s** via Buchwald-Hartwig coupling reaction of **24** and **112s** in BTF.

Similarly to the precursors, the appearance of the tetrahydropyridine signals in the ^{1}H NMR spectrum could be interpreted to give some indication of the likely conformation of the ring. The signals appeared very similar to the tetrahydropyridine precursor **112s**, although the signals for the methylene groups adjacent to the tetrahydropyridine nitrogen atom were shifted downfield due to the deshielding effect of the aromatic quinoline ring system. The signals corresponding to the hydrogen atoms in the tetrahydropyridine ring were substantially broadened, indicating slow interconversion between ring conformations on the NMR timescale and therefore a substantially planarised ring conformation as anticipated (Figure 57A). The appearance of the signals for the heterocyclic ring were compared to the 6-substitituted 2-chloroquinoline derivative **82x** with a 4-benzylpiperidine substituent (Figure 57B) and a **106s** with a 4-benzylidenepiperidine substituent (Figure 57C). Whereas the distinct axial and equatorial hydrogen signals for the benzylpiperidine compound **82x** indicate a chair-like conformation of the heterocyclic ring, the NMR signals for the alkene derivatives **106s** and **107s** show less signals and no distinct axial and equatorial hydrogen atoms. The broadness of the signals indicates there is slow interconversion between the ring conformations on the NMR timescale, and these observations demonstrate the heterocyclic rings for the alkene compounds **106s** and **107s** are substantially planarised compared to **82x**. Between the two compounds with substantially planarised heterocyclic rings, there is a still significant structural variation due to the freely rotating benzyl group of the tetrahydropyridine compound **107s**. In contrast, the planar and asymmetric alkene bridge of **106s** has one fewer rotatable bonds and the spatial position of the substituted benzene ring relative to the quinoline ring is limited compared to **82x** and **107s**.

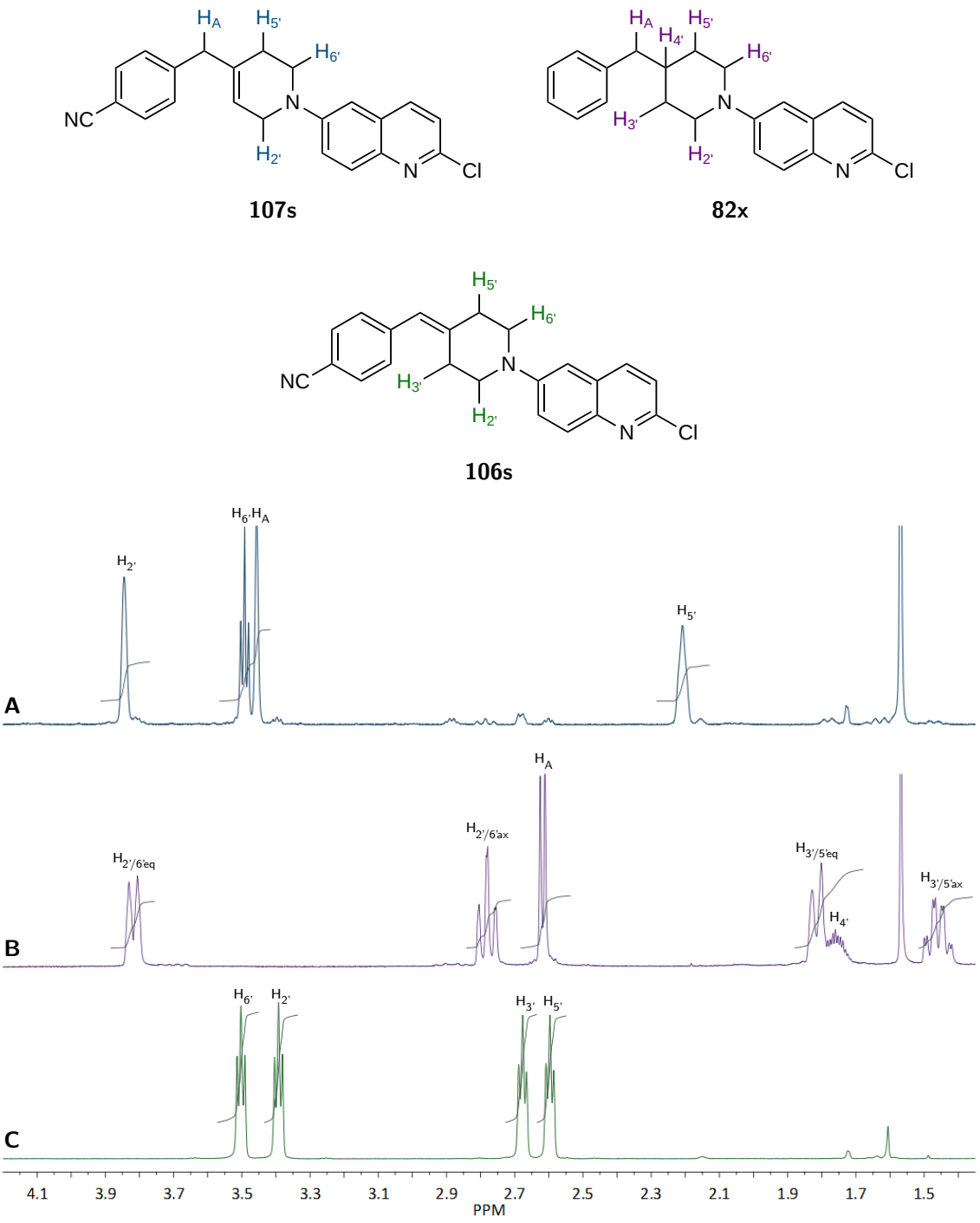
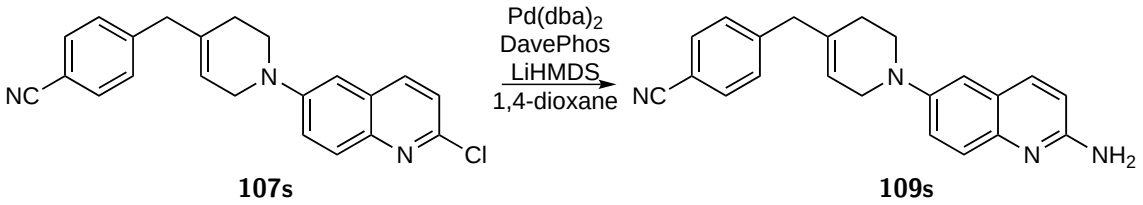


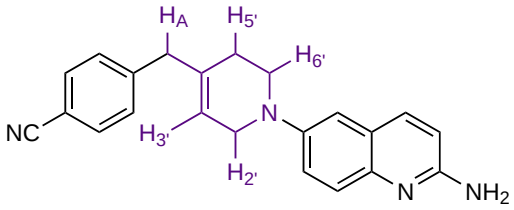
Figure 57: Comparison of ^{1}H NMR spectra for structurally different 6-position extended 2-chloroquinoline compounds. A: Tetrahydropyridine substituted 2-chloroquinoline product **107s**, B: 4-benzylpiperidine substituted 2-chloroquinoline product **82x**, and C: 4-benzylidenepiperidine substituted 2-chloroquinoline **106s**.

The 2-chloroquinoline **107s** was treated with LiHMDS and reacted under Buchwald Hartwig amination conditions to give an impure mixture of products containing the corresponding 2-aminoquinoline compound **109s** (Scheme 79). The products could not be separated using column chromatography, and therefore the ^{1}H NMR spectrum of the crude mixture was instead analysed to determine the principal components of the reaction mixture (Figure 58).

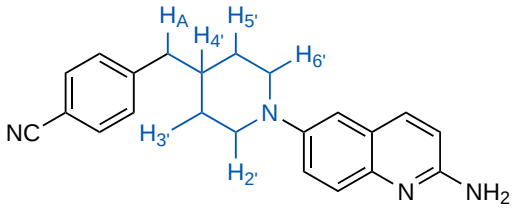


107s **109s**

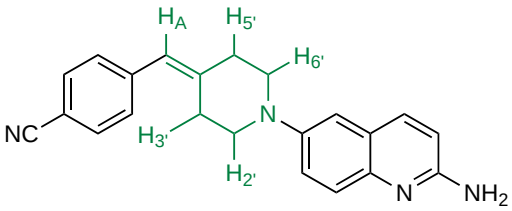
Scheme 79: Buchwald-Hartwig amination of benzonitrile extended 2-chloroquinoline derivative with a 6-position tetrahydropyridine substituent (**107s**) to give the corresponding 2-aminoquinoline product **109s**.



109s



19s



102s

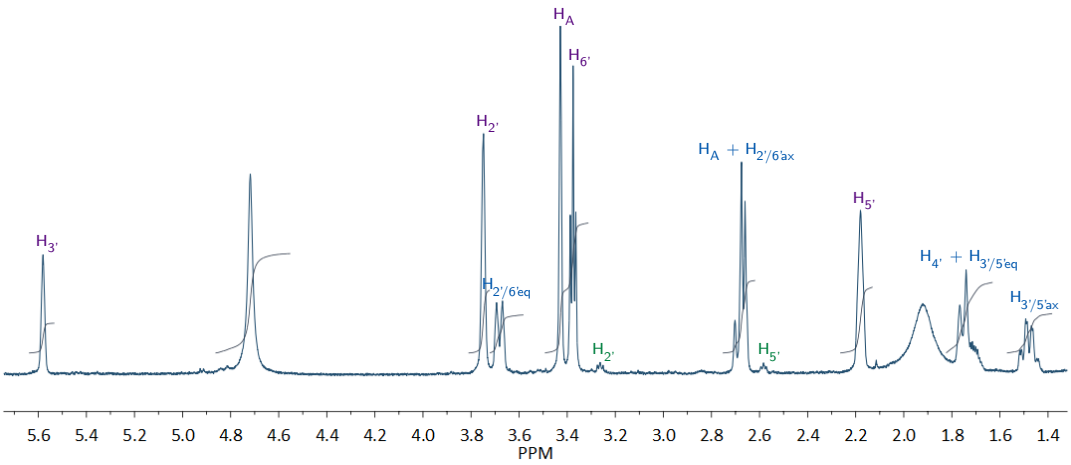


Figure 58: Upfield region (δ 1.3 ppm - 5.8 ppm) of ^{1}H NMR spectrum of crude mixture after attempted amination of tetrahydropyridine extended 2-chloroquinoline, and structures of the proposed products. The NMR signals corresponding to each product are labelled in purple for **109s** and blue for **19s**, and the non-overlapped signals for **102s** are labelled in green. The NH_2 signals for the three compounds are overlapped and not labelled (broad signal at 4.73 ppm).

It was determined that the major product was the desired 2-aminoquinoline **109s**, with a 6-position tetrahydropyridine substituent. The ^{1}H NMR signals consistent with each of the methylene groups of the tetrahydropyridine substituent were present, and the broad alkene signal at 5.58 ppm was also evident and characteristic of a tetrahydropyridine product. The

success of the 2-position amination reaction was evident due to the clear upfield shift of the H_3 doublet signal compared to the 2-chloroquinoline reagent, due to the electron-donating amino group.

The second major product was in some respects similar to the desired product, and also had an upfield H_3 doublet signal consistent with another 2-aminoquinoline product. Instead of the broad 2H signals for the methylene groups of the tetrahydropyridine product, however, the pattern of signals in the upfield region of the ^{1}H NMR spectrum was diagnostic for a chair-like conformation of a piperidine ring. From this, it was deduced that a significant amount of the tetrahydropyridine structure had been reduced under the relatively harsh amination reaction conditions in a sealed tube, therefore yielding the 4-piperidine compound **19s** which had been synthesised previously.

A small amount of a further minor product was also observed in the crude ^{1}H NMR spectrum. A small singlet signal at 6.38 ppm indicated that some isomerisation may have occurred to give the benzylidenepiperidine compound **102s**. While most of the signals corresponding to this minor product are overlapping with signals for the major products, the triplet-type signals present at 2.59 and 3.27 ppm are consistent with the signals expected for the substantially planarised 4-piperidine ring with a benzylidene substituent, therefore these observations strongly support that this minor product is indeed the compound **102s**.

Each of these compounds are very structurally similar and therefore, although it was clear the desired product had been synthesised, the compound **109s** could not be isolated or assayed with the Tec SH3 domain. The crude NMR spectrum did indicate that the conformational structure of the 6-position substituent was as expected, with a substantially planarised heterocyclic ring. If a more effective and selective synthesis of this type of tetrahydropyridine compound were developed, the hypothesis that a 6-substituted 2-aminoquinoline with a substantially planarised heterocyclic ring and a freely rotating benzyl substituent would interact differently with the Tec SH3 domain could then be tested.

2.4 Binding studies of 6-position extended 2-aminoquinoline derivatives

2.4.1 Assay aims and proposed method

The binding activity of the 2-aminoquinoline derivatives with the *murine* Tec SH3 domain in previous studies had been investigated using either NMR chemical shift perturbation assays or Fluorescence Polarisation (FP) assays.[52,50,54,53] Both of these methods can give valuable information regarding the binding position or competitive binding activity of the ligand for the Tec SH3 domain, however given the large number of compounds prepared in this work it was determined that an alternate method for higher-throughput screening of the small-molecule ligands would be preferable. Surface Plasmon Resonance (SPR) assay methods have emerged as a useful tool for screening of protein interactions, and while this gives less information on the nature of the binding interaction (compared to NMR assays, for example) the method can be used to more rapidly and simply identify 'hit' compounds which interact with the protein target. A 'hit' compound is, for the purpose of this investigation, any ligand determined to bind with similar or improved binding affinity (measured as the equilibrium binding dissociation constant K_d) compared to the previous lead compound, **15**, and therefore determined to be of interest for further investigation or interpretation of the binding activity.

In this project, an initial SPR assay 'screen' was first used to investigate whether any of the synthesised 2-aminoquinoline compounds bound with improved affinity compared to the previously determined lead compound **15**. The screen tests a general concentration range which would determine a rough binding dissociation constant for compounds which bind with K_d less than approximately 20 μM. The accuracy of the binding isotherm and K_d determination is unreliable for K_d outside this range due to the extrapolation required. For K_d values less than 5 μM the screening method was also less accurate due to the limited number of data points at lower concentrations, which means that the screening K_d for some compounds does not reflect the true K_d value, and therefore should not be interpreted as an accurate measurement of the binding affinity.

For any compounds which did appear to have improved binding activity compared to the previous lead compound, the SPR method was then used to determine the binding dissociation constants with an optimised method for the indicated K_d value and measurements repeated in triplicate. Ultimately, it was desired that this would identify a sufficiently strongly binding ligand which could then be used to determine the 3D structure of the protein-ligand complex via alternate methods, either NMR assays or crystallographic methods. However, even without identification of such a strongly binding ligand, the information gained from this SPR method would enable comparison of the binding affinity for the different ligand structures and therefore some interpretation of the structure-activity relationship (SAR). This information could then

be used in further studies to design 2-aminoquinoline ligands which would be predicted to bind even better than those prepared in this work, and therefore lead to the goal of a strongly binding 2-aminoquinoline ligand.

2.4.2 Screening method: Surface plasmon resonance (SPR) assays

The testing of biological interactions using this method exploits the principle of surface plasmon resonance at an interface between a gold surface, known for having a high number of surface plasmons, and a glass prism (Figure 59A). At a certain critical angle of light on a glass prism, photons are internally reflected and come into resonance with the surface plasmons of the gold layer. Due to the excitations of the surface plasmons of the gold layer at resonance, the light at the SPR angle is absorbed and therefore it is observed that the reflected light has a lower intensity.

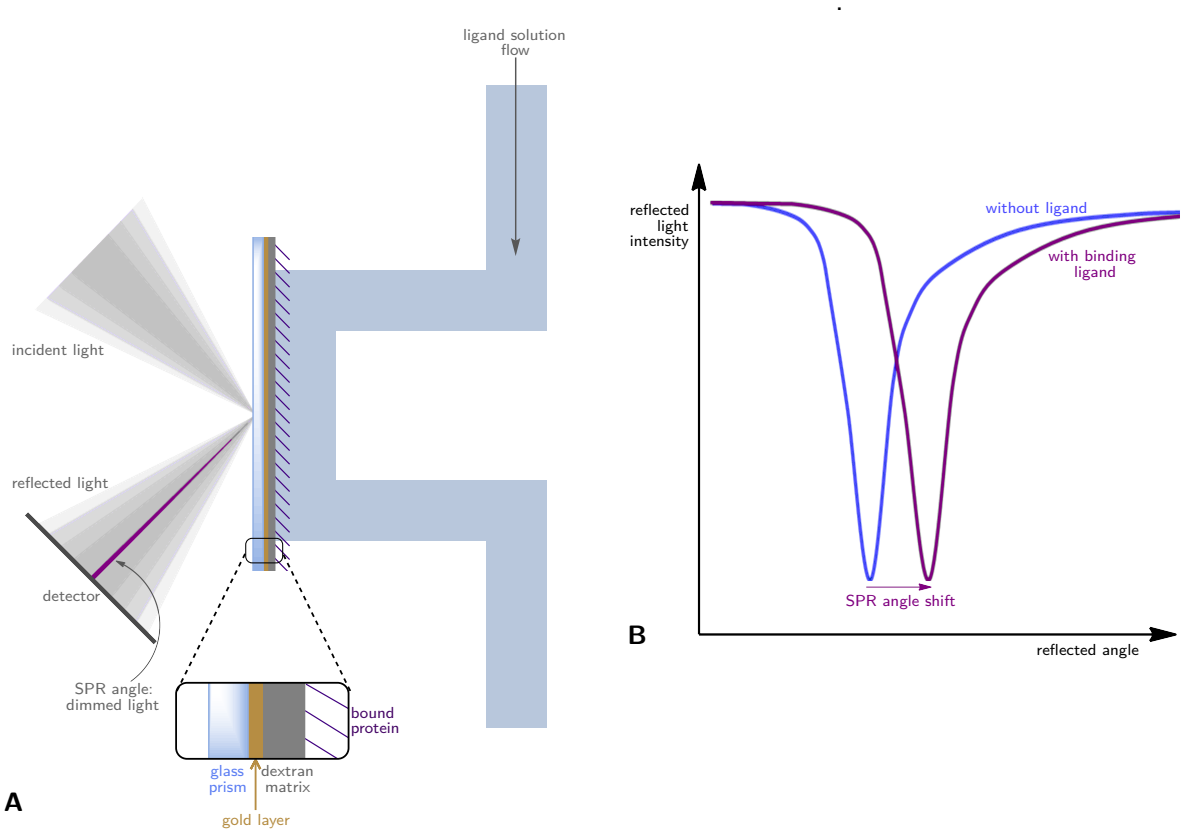


Figure 59: Surface plasmon resonance as applied to sensing of biological interactions. A: Experimental set-up for measurement of SPR angle, solutions passed over sensor surface with bound target protein. B: Change in SPR angle measured upon binding of small-molecule ligand to bound target protein. (Adapted from GE Life Sciences, 2015.[80])

The angle of incident light required for surface plasmon resonance is affected by the mass concentration near the gold surface.[81] Using this feature, if the target SH3 protein is attached to the gold surface then binding of a small-molecule ligand to form the SH3-ligand complex

will result in an increase in mass concentration near the gold surface, and therefore a change in SPR angle will be observed (Figure 59B). This change in SPR angle upon addition of ligand is referred to as the 'response' and is quantified in response units (RU).[82] The change in response is directly proportional to the mass concentration at the gold surface and can therefore be used to investigate the kinetics or affinity of the protein-ligand interactions.[83,84]

Unlike NMR assays or FP assays which require modified protein or peptides in order to measure binding (nitrogen-15 labelled SH3 domain, or fluorescence tagged proline-rich peptide, respectively), the SPR assay method does not require any modifications to the protein target or the small-molecule ligand in order to measure the relative binding affinity, which is a significant experimental advantage. Instead, the sensor surface with attached SH3 domain target was prepared using what is referred to as the 'amine-coupling method' (Figure 60). By this method, the sensor chip (comprised of the glass prism coated with a gold layer) was obtained with a dense carboxymethylated dextran matrix coating the surface, and the exposed carboxyl groups were first reacted with NHS to give reactive succinimide esters. The Tec SH3 protein contains amino acid residues with nucleophilic groups, and the NHS esters react with these nucleophilic groups or the *N*-terminal amine so that the target SH3 protein is covalently attached to the sensor surface. After successful immobilisation of the SH3 protein, treatment with ethanolamine was used to quench any remaining unreacted NHS esters.

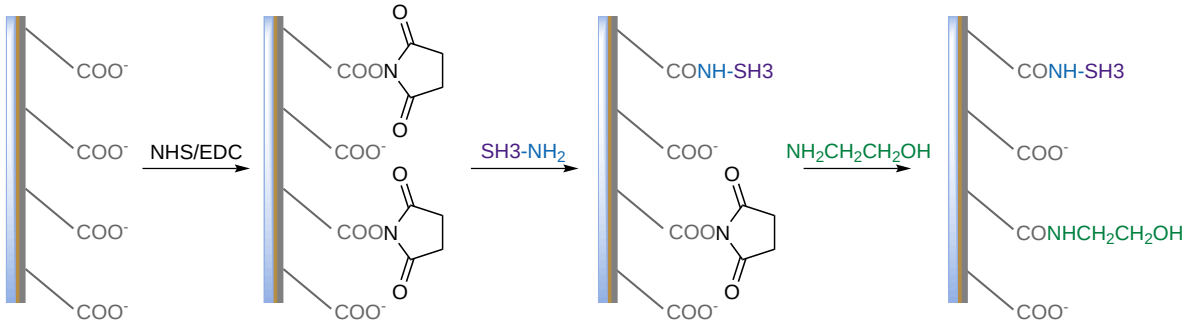
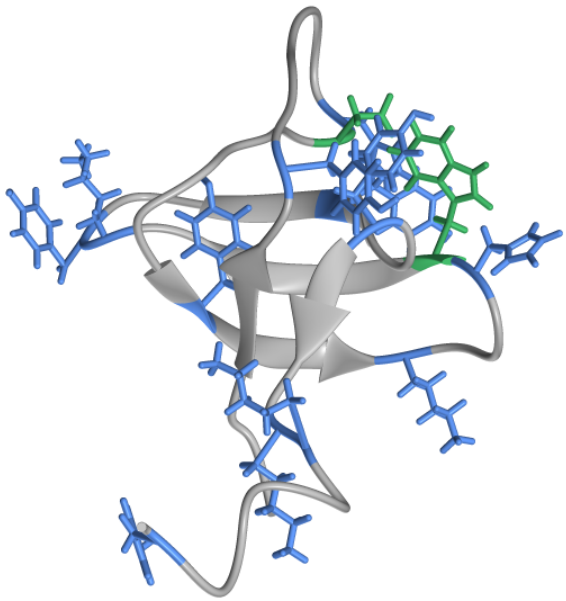


Figure 60: Preparation of the SPR sensor surface with covalently attached Tec SH3 domain, using a gold-coated glass prism (depicted in blue, yellow) with carboxymethyl-functionalised dextran matrix (grey). Adapted from Johnsson *et al.* (1991).[85]

Using this method, it was considered preferable to utilise the GST-SH3 fusion protein as the immobilised protein target instead of isolated SH3 domain. The GST-SH3 fusion protein is simpler to purify, and in this case the GST protein was used as a reference protein for the SPR binding assays. Previous studies investigating the binding of 2-aminoquinoline ligands to the Tec SH3 domain had also used the GST-SH3 fusion protein for assays.[50]

While the label-free method for attaching the SH3 domain protein to the sensor surface is advantageous and simpler compared to methods which require labelled protein, it also imposes some limitations on the binding interactions which may be detected. The 'amine-coupling'

method does not necessarily attach exclusively through amine groups of the lysine side-chains and the *N*-terminus amino group, as NHS esters are known to react with several nucleophilic groups of amino acid side-chains, including the thiol group of cysteine, the imidazole of histidine, and the phenoxy group of tyrosine.[86] Given that several residues containing these nucleophilic groups are present in the GST-SH3 fusion protein (Figure 61), the covalent attachment of the target SH3 domain to the sensor surface could occur through several different residues and therefore the orientation of the bound SH3 domain would not be consistent. Some of the nucleophilic side-chains are near to the binding region targeted by the 2-aminoquinoline ligands, and therefore binding through these residues would potentially hinder the ability of the small-molecule ligands to bind effectively during the SPR assay.



EIVVAM**Y**DFQA TEA**HD**LRLER GQE**Y**IILE**K**N DL**HW**WRARD**K** **Y**GSEG**Y**IPSN **Y**VTG**KK**

Figure 61: Structure of the Tec SH3 domain target and nucleophilic residues available for coupling to sensor surface. Primary sequence of *murine* Tec SH3 domain with residues known to be important for binding of 2-aminoquinolines (W216 and D196) highlighted in green, and residues with nucleophilic side chains known to react with NHS esters shown in blue. Ribbon structure of *murine* Tec SH3 domain shown with the side chains visible for highlighted residues only.

The dense carboxymethyldextran matrix on the sensor chip enables a high concentration of the protein target to be immobilised on the sensor surface. Even though the coupling of the SH3 domain target to the activated NHS esters may have been non-selective, the high concentration of immobilised protein should ensure that a large amount of the protein target is still accessible and available for binding to the small-molecule ligands. A small-molecule ligand known to bind to the SH3 domain target was used as a positive control to ensure consistency between the assays and immobilisations, and in each case the measured SPR response demonstrated that the ligand could successfully bind to the immobilised GST-SH3 fusion protein.

The 2-aminoquinoline ligand compounds were all prepared as solutions in 5% DMSO/ 1 x PBS buffer of increasing concentration up to 100 μM. The use of DMSO was intended to aid solubility of the small-molecule ligands for the SPR assays, however the NMR assays used previously were run in a solution of 10% DMSO, and therefore there was an added limitation upon the lipophilicity of ligands which could be tested using this SPR method. For the ligand solutions, the SPR response was measured as the solutions were passed over the protein chip. Higher concentrations of ligand bound to the protein gave a larger SP response at the protein surface. The assays resulted in a sensorgram for SP response over time for each concentration (for example, Figure 62). In each case the sensorgram showed that after injection of the ligand solution (point A) steady-state binding was rapidly achieved (point B). After sufficient time to ensure the response was stable, the sensor surface was washed with buffer to remove all bound ligand (point C). The studied 2-aminoquinoline ligands were rapidly removed from the GST-SH3 protein, returning the sensorgram to baseline level (point D).

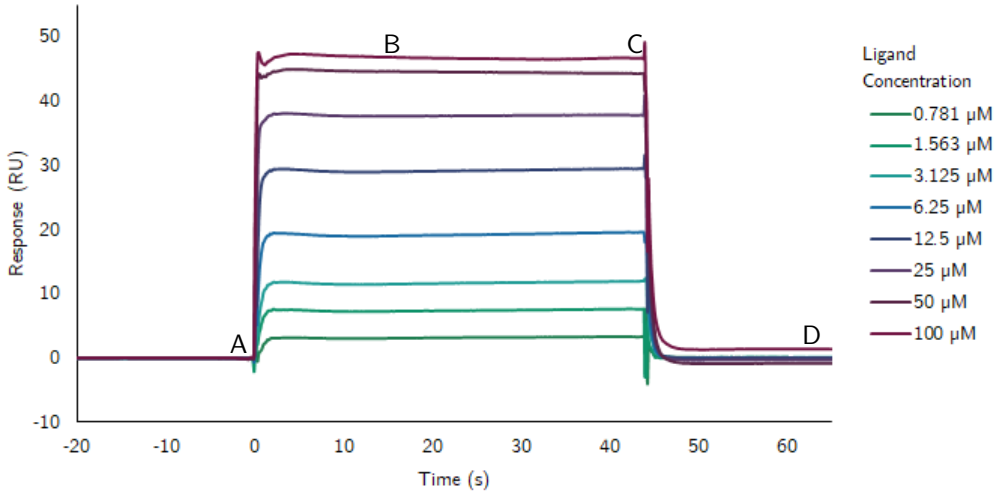


Figure 62: Typical SPR assay sensorgrams used for determination of equilibrium dissociation binding constant K_d for a small-molecule ligand. Example shown is for compound **22a**.

Steady-state or equilibrium binding was observed at each concentration of 2-aminoquinoline ligand, giving a region where the response is consistent and therefore the rate constants for binding and dissociation of the protein-ligand complex are equal. The steady-state response (R_{eq}) for each sensorgram was therefore plotted against the ligand concentration (C) to generate the binding isotherm (Figure 63), and nonlinear regression fitting could then be used to obtain the K_d value according to the following model for a 1:1 protein-ligand binding interaction:

$$R_{eq} = \frac{C.R_{max}}{C + K_d} + RI \qquad (2)$$

The nonlinear regression analysis determined fitted values for the response upon saturation of

protein binding sites (R_{max}), equilibrium binding dissociation constant (K_d) and the response offset due to the bulk refractive index in the sample (RI).[87,88] As demonstrated by Equation 2, the K_d value is the concentration of 2-aminoquinoline ligand required to achieve half the maximum response (R_{max}), or occupy half of the saturation SH3 binding sites.

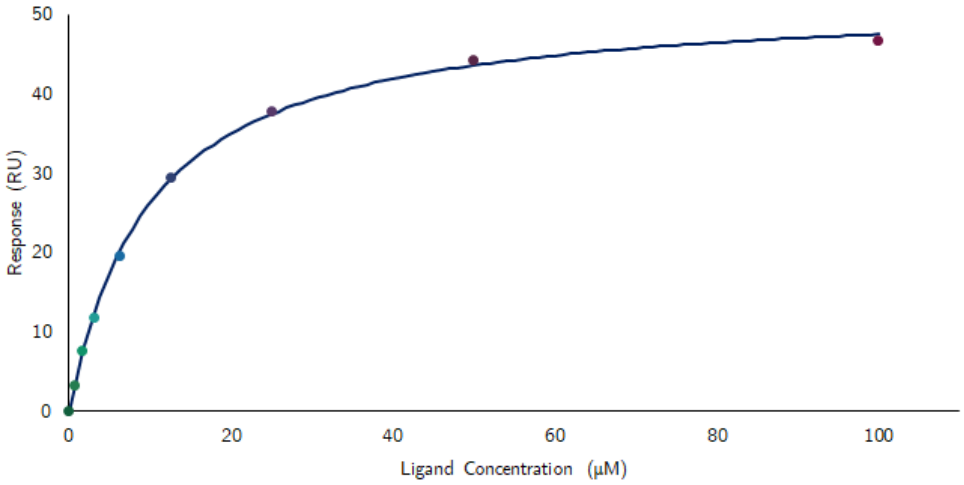
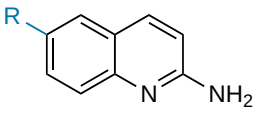
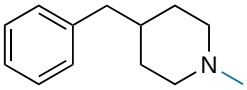
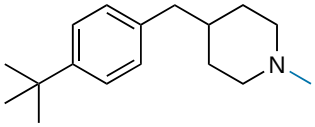
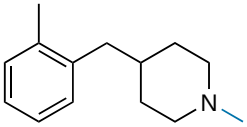
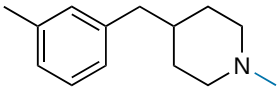
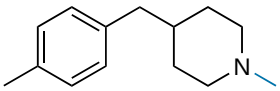
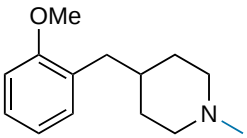
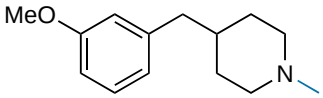
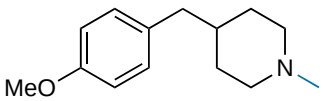
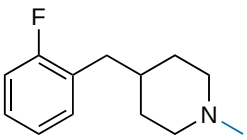
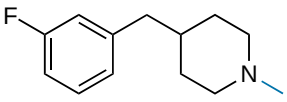
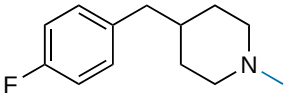


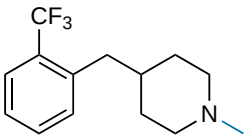
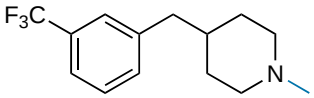
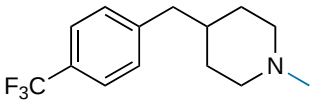
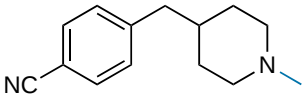
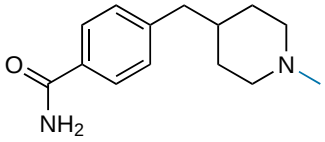
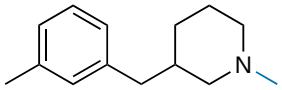
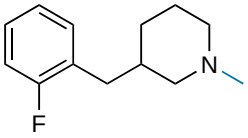
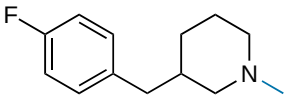
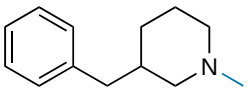
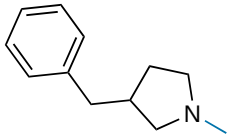
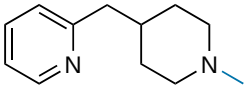
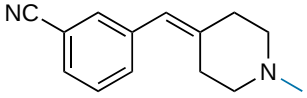
Figure 63: Typical binding response curves for SPR assay used for determination of dissociation binding constant K_d. Example shown is assay of ligand **22a** with Tec GST-SH3 fusion protein.

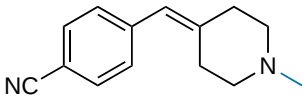
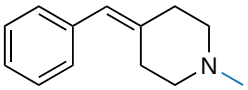
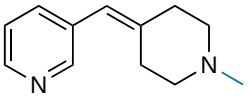
All prepared 2-aminoquinoline ligands were initially screened using standard concentrations (up to 100 μM) to determine the screening K_d value, and then repeated in triplicate for the 'hit' compounds to determine the assay K_d values (Table 22). The range of concentrations tested to determine the assay K_d values were optimised to avoid extrapolation, especially for the tighter binding ligands where saturation binding was typically achieved at lower concentrations.

Table 22: Results of SPR assays for 6-position substituted 2-aminoquinoline ligands.



R =	Compound	Screening K_d (μM)	Assay $K_d \pm$ SD (μM)
	**15**	9.1	27 ± 11^{b}
	**19a**	*insoluble*	
	**19b**	29.3^{b}	
	**19c**	$> 50^{b}$	
	**19d**	9.4^{c}	
	**19e**	$> 20^{b}$	
	**19f**	$23.7^{a,b}$	
	**19g**	15.4^{b}	
	**19h**	17.8^{c}	
	**19i**	13.2	
	**19j**^{c}	13.9^{c}	

R =	Compound	Screening K_d (μM)	Assay $K_d \pm$ SD (μM)
	**19n**	$> 30^{b,c}$	
	**19o**	$> 30^{b}$	
	**19p**	$> 50^{b,c}$	
	**19s**	1.7^{a}	2.0 ± 0.5
	**101**	1.9^{a}	2.0 ± 0.1
	**20c**	16.4	
	**20h**	$5.2^{a,b}$	$19 \pm 7^{a,b}$
	**20j**	$20.6^{a,b}$	
	**20x**	13.0	
	**21x**	9.6	9.7 ± 0.3^{a}
	**22a**	5.8	5 ± 1
	**102r**	16.7	

R =	Compound	Screening K_d (μM)	Assay $K_d \pm$ SD (μM)
	**102s**	2.9	2.2 ± 0.7
	**102x**	9.0	20 ± 3
	**108b**	1.5[a]	1.9 ± 0.1

[a] Highest concentration data point removed due to precipitation or aggregation of compound under assay conditions. [b] Response-concentration curve not at plateau, saturation binding not achieved. [c] Response too low for saturation binding.

2.4.3 Results of screening.

As this was a new assay method used for the investigation of small molecules binding the the Tec SH3 domain, it was not assumed that the K_d values determined by the SPR method could be directly comparable to the K_d values reported for previous compounds which were determined by the NMR chemical shift perturbation assay method. The compound **15** had previously been assayed using the NMR assay method and this determined a K_d value of 9 μM.[52] The same compound was therefore assayed with the Tec SH3 domain using the SPR method, and although initially the screening method gave a consistent K_d value this was difficult to replicate and a large range of values were obtained ($K_d = 27 \pm 11$ μM). The high degree of variability with results for this compound meant the lead compound was not an effective positive control which could be used for comparison of binding affinity with the novel compounds. The reasons for the lack of reproducibility were not clear, however it was noted during the synthesis of the majority of the benzylpiperidine-extended derivatives, including **15**, that the 2-aminoquinoline products appeared to degrade over time, and in particular degradation occurred more rapidly when exposed to light. This degradation was not noted in the previous studies,[52] and changes in the measured K_d value over time had not been examined previously, so the impact of this upon the results of the NMR assays was not clear. For the SPR method, however, it was evident that the K_d value could not be effectively replicated.

In contrast, the novel 2-aminoquinoline ligand **22a** with a pyridinylmethylpiperidine substituent did not appear to have the same rapid decay in light. Binding assays of this compound using the SPR method were much more consistent with each other and consistent over time. The

observations indicate that the pyridinyl compound may be less susceptible to degradation over time compared to the previous lead compound, which is a very favourable incidental discovery for this project as compounds which degrade rapidly are obviously difficult to study for bioactivity and, for further applications, would not be useful as potential drug compounds. It was found over a series of assay runs that when the lead compound **15** and the novel ligand **22a** were both assayed in succession, the novel compound always had a lower K_d value, and overall the results were much more consistent ($K_d = 5 \pm 1$ μM). From this, it was determined that **22a** was likely a stronger binding ligand than the lead compound, and due to the consistency of results **22a** was subsequently used as the positive control for the SPR assays.

While the screening identified seven novel 2-aminoquinoline compounds which appeared to bind with improved binding affinity compared to the previous lead compound, the hit rate was quite low despite the similarities in structure. The differences indicate that the 6-position quinoline substituent has a very significant impact upon the strength of the binding interaction with the Tec SH3 domain, with the potential for the strongest binding small-molecule ligands identified to date (including **101** and **108b**) or dramatically reduced binding affinity (**19c** and **19p**).

Substituted 4-benzylpiperidines

The largest subset of novel compounds tested were 2-aminoquinoline compounds with a substituted 4-benzylpiperidine substituent, based upon the 4-benzylpiperidine extended lead compound **15**. Unsurprisingly, the largest compound tested, with a bulky *t*-butyl substituent, was insoluble under the SPR assay conditions. This compound (**19a**) had a calculated* logP value of 6.27, whereas the calculated logP values for the other compounds were below 5.6 and appeared to have sufficient solubility under the SPR assay conditions. The majority of the substituted 4-benzylpiperidine ligands were found to bind with similar or weaker binding affinity compared to the lead compound.

The size of the benzyl substituent did not appear to be a significant factor affecting the strength of the binding interaction with the Tec SH3 domain. Correlations between the substituent position and the binding affinity were not clearly apparent, although ligands with substituents at the 2-position of the benzene ring mostly tended to have weaker binding affinity compared to the 3-position and 4-position substituted compounds with the same substituent. These results indicated that the substituent was not affecting the interaction due to bulk or size making an additional contact with the Tec SH3 domain upon binding, although the weaker binding affinity for the *ortho*-substituted benzene rings may indicate some unfavourable steric effects upon the binding interaction due to the shape of the ligand. Instead, the results indicate

*Calculated logP values were obtained using the Marvin chemical editor and calculator, available from ChemAxon https://www.chemaxon.com.

that other characteristics of the various benzyl substituents affected the binding interaction and gave the observed differences in activity.

The two strongest binding compounds identified were the benzonitrile ligand **19s** and the benzamide ligand **101** (K_d = 2.0 ± 0.5 μM and 2.0 ± 0.1 μM respectively). These were the only ligands with benzyl substituents which were electron-withdrawing by resonance, indicating that the electron density in the aromatic ring was most likely the major contributing factor to the significantly improved binding interaction. Interestingly, the trifluoromethyl-substituted ligands **19n**-**19p** exhibited significantly weaker binding affinity compared to the other 4-benzylpiperidine ligands, even though this is also an electron-withdrawing substituent. The *para*-substituted derivative **19p** in particular had a dramatically weaker binding affinity, outside the range which could be measured using the SPR assay method. This does indicate that electronic effects of the substituents may not be sufficient to explain the difference in affinity, but the large difference in lipophilicity of these substituents likely also contributes to the observed difference. It is expected that the trifluoromethyl-substituted compounds would be less soluble under the assay conditions compared to more hydrophilic benzamide and benzonitrile compounds, and the low response values observed in the assay results for **19p** may indicate that solubility was a factor in the weaker binding affinity measured. Other ligands with fluoro or methyl substituents also resulted in low response readings or observed precipitation of the small molecule ligand at higher concentrations.

Solubility of the ligands under biologically relevant conditions was previously noted as a significant challenge to developing these small-molecule ligands targeting the Tec SH3 domain. Incorporating hydrophilic substituents was one strategy proposed to improve the water solubility of the extended 2-aminoquinoline ligands, and the results of these assays demonstrate that benzylpiperidines with hydrophilic substituents are not only sufficiently soluble under the assay conditions, but also appear to have improved binding affinity compared to the other tested ligands. This is a very favourable result for the overall goal of finding more effective and more drug-like ligands for the Tec SH3 domain, unnecessitating any requirement to compromise the strength of the binding interaction in order to improve the aqueous solubility of the compounds.

Structural analogues of 4-benzylpiperidines: 3-benzylpiperidines and 3-benzylpyrrolidines

The 3-benzylpiperidine and 3-benzylpyrrolidine derivatives were initially proposed to investigate whether the favourable binding interactions identified by the lead compound **15** could be further optimised by changing the relative positions of the benzyl substituent and the quinoline core structure. These compounds were synthesised as a racemic mixture, and the stereoisomers were not separated for the purposed of the assays. As a result, these assays contain two structurally different isomers which would be expected to have different interactions with the

3D protein target. If any improvement in the binding affinity was observed then this would indicate that at least one of the stereoisomers had improved binding affinity compared to the lead compound, and therefore further investigation would be warranted. The synthetic pathway developed for the analogous 4-benzylpiperidines was less effectively applied to the synthesis of the 3-benzylpiperidine and 3-benzylpyrrolidine targets and could not be sufficiently optimised, therefore a smaller range of these compounds was available for investigation of the binding affinity.

The SPR assay results for these ligands did not indicate any improvement in the strength of the binding interaction compared to the lead compound, with a range of measured K_d values between 9 and 21 μM, compared to $K_d = 9$ μM for the lead compound **15**, as determine by the SPR assay. The derivatives with unsubstituted benzyl groups displayed very little difference to the 4-benzylpiperidine analogue, with $K_d = 13$ μM for the 3-benzylpiperidine (**20x**) and $K_d = 10$ μM for the 3-benzylpyrrolidine ligand (**21x**), and similar results were observed with the substituted benzylpierpidine assayed.

None of the 3-benzylpiperidine or 3-benzylpyrrolidine compounds bound with significantly improved binding affinity compared to the lead compound, and due to the difficult and low yielding synthesis of these types of compounds it was concluded that further investigation of these types of piperidine compounds was not likely to yield any substantial progress towards achieving the project goals. Nevertheless, once the 3D structure of the SH3 domain complex with a 6-position extended 2-aminoquinoline is obtained, the binding model might indicate that further improvements may be made with these asymmetric piperidine type structures and further investigation may then be warranted as informed by the additional structural information gained for the binding region.

Structural analogues of 4-benzylpiperidines: 4-benzylidenepiperidines

The 4-benzylidenepiperidine ligands were other structural analogues of the 4-benzylpiperidine lead compound, and were primarily considered to be interesting targets due to the substantially planarised piperidine ring conformation and therefore different 3D structure of these compounds. The bridging alkene instead of the methylene group also restricts the free rotation of the benzyl group, and therefore investigating the impact of this upon the binding interaction of the ligands with the Tec SH3 domain would give useful information on the nature of the binding interaction.

The binding affinities of the benzylidene ligands **102x** and **102s** were directly compared to the benzyl analogues **15** and **19s** respectively. The assay results for the benzylidenepiperidine and benzylpiperidine analogues were comparable (within error) in each case, and it was evident that there was no significant improvement in the strength of the binding interaction achieved by inclusion of the more planarised benzylidene group. The results therefore demonstrate that the alkene bridging group is not a favourable structural change from the freely rotating

methylene bridge.

Comparison of structurally different benzylpiperidine-type ligands

The relatively poor binding of the benzylidenepiperidine ligands is likely due to either restricted rotation of the benzyl group, or due to the comparatively planarised piperidine ring conformation which would affect the position of the benzylidene substituent.

As similar results were obtained for the 3-benzylpiperidine and 3-benzylpyrrolidine ligands (**20x** and **21x** respectively) compared to the lead compound, this may indicate that the position of the benzyl substituent has little impact upon the strength of the binding interaction. Therefore, it would be expected that the restricted rotation of the benzyl group is predominantly causing the reduced strength of the binding interaction, rather than the piperidine ring conformation.

In order to investigate the effect of planarised piperidine ring conformations upon binding, the tetrahydropyridine-extended 2-aminoquinoline compound **109x** would be a highly valuable target (Figure 64). NMR studies of the tetrahydropyridine compounds isolated as part of this project demonstrated that the piperidine ring is substantially planarised, similar to the benzylidenepiperidine derivatives, but in contrast the benzyl group is freely rotating and therefore more similar to the benzylpiperidine derivatives.

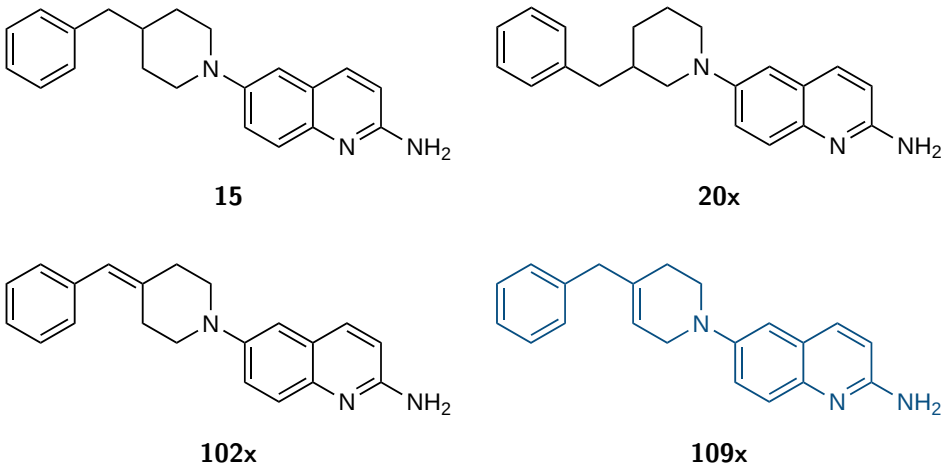


Figure 64: Structurally different extended 2-aminoquinoline compounds, which could be investigated to probe the effects of piperidine ring conformations and free rotation of the benzyl substituent upon the strength of SH3 domain binding interactions. Compounds **15**, **20x** and **102x** were tested for binding affinity, and the proposed structure **109x** would be required for further investigation.

The synthesis of the benzonitrile analogue of this compound **109s** was attempted but the product could not be purified and tested for binding activity (see Scheme 79, page 111), and the synthetic method would not be generalised to yield the unsubstituted derivative **109x**. Tetrahydropyridine compounds such as these would be highly valuable compounds used to

explore the nature of the binding interactions with the Tec SH3 domain, and therefore would be worth investigating if an effective and selective synthetic method was at some point developed to achieve these types of structures.

Further to the benzylidenepiperidine compounds which were directly compared to the analogous benzylpiperidines, the pyridinylmethylpiperidine derivative **22a** had been noted as a comparatively stable ligand with an improved binding affinity compared to the lead compound, and therefore the binding affinity of the similar pyridinyl-extended methylidenepiperidine compound **108b** was also investigated as a comparison. It was found that this compound had a significantly stronger binding affinity compared to the lead compound, and was among the strongest binding ligands investigated to date with a measured K_d value of 1.9 ± 0.1 μM. The assay results for the 4-benzylpiperidine and 4-benzylidenepiperidine ligands indicated that a methylene bridge may be preferable and therefore it was proposed that the 3-pyridine variant of **22a** might have even stronger binding affinity for the Tec SH3 domain, but this target was not isolated in sufficient yield and purity to be assayed.

2.4.4 Results of SPR assays and insight into binding model

The investigation of 4-benzylpiperidine extended 2-aminoquinoline ligands and a range of structural variants of these compounds identified several novel compounds which bound with significantly improved binding affinity for the Tec SH3 domain using SPR assays. Of particular interest were the 4-benzylpiperidine compounds with a substituent which was electron withdrawing by resonance (benzonitrile **19s**, and benzamide **101**) and the pyridinyl-extended piperidine compounds **22a** and **108b** (Figure 65).

The stronger binding affinity observed for these particular compounds indicates that an electron poor aromatic ring improves the strength of the interaction accessed by the benzylpiperidine substituent, as pyridines are electron poor compared to benzene rings and the nitrile or cyano benzyl substituents are electron-withdrawing by resonance. While the precise interaction with the SH3 domain responsible for this change in binding affinity is unknown until a 3D structure of the protein-ligand complex is determined, this relationship between electron density of the aromatic system and the strength of the binding interaction may be useful in guiding the design of further target compounds, and electron donating substituents in particular should be avoided.

Additional size of the 6-position substituent is not needed to improve the strength of the binding interaction, as evidenced by the pyridinyl compounds **22a** and **108b**. It is therefore expected that adding substituents does not make a further favourable contact with the Tec SH3 domain surface, and instead the improvement observed in binding affinity is simply the result of improving the strength of the binding contacts that were being accessed by the

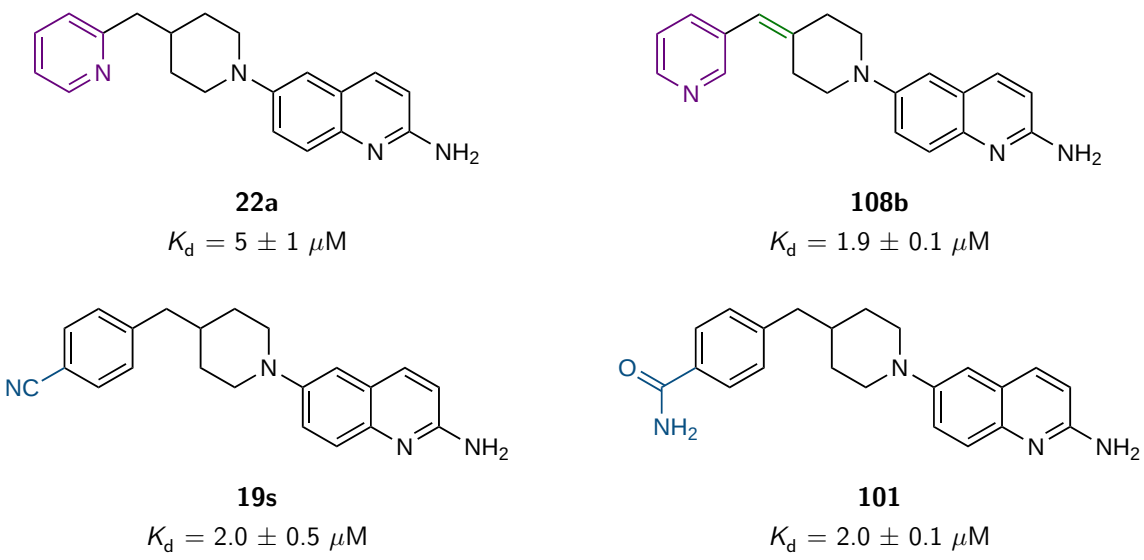


Figure 65: Structures of strongest binding 2-aminoquinoline ligands for the Tec SH3 domain, as determined using SPR assays. Changes in structure compared to previous lead compound **15** are highlighted.

benzylpiperidine lead compound. Additionally, while additional size is not required it also does not seem to be a hindrance to the binding interaction. The *para*-substituted benzonitrile and benzamide ligands **19s** and **101** are larger than the pyridines, but the improvement in the strength of the binding interaction indicates that there is space available to extend the ligand in this direction without steric clashes of the bound ligand with the protein surface which would negatively impact the strength of the binding interaction. This suggests that addition of even larger 6-position substituents to the 2-aminoquinoline ligands may be accommodated by the binding surface although it is not yet clear whether any further favourable binding opportunities are available.

Perhaps the most important result, from the perspective of developing more effective ligands with potential use in biological systems, was the synthesis and discovery of several stronger binding small-molecule ligands which each contain more hydrophilic structures than the lead compound **15**. The replacement of a benzene ring with a less lipophilic pyridine ring and the incorporation of hydrophilic substituents were strategies proposed to improve the aqueous solubility of the Tec SH3 domain ligands, which was an important issue which needed to be resolved due to the largely hydrophobic core structure of the lead compound developed in previous work. These compounds not only have reduced lipophilicity and therefore more drug-like characteristics, but this was achieved while still improving the binding affinity of the small-molecule ligands for the Tec SH3 domain.

The success of these strategies demonstrates that improving the binding affinity of small-molecule ligands for an SH3 domain, or even a protein-protein interaction target more generally, can occur simultaneously with developing ligand with more drug-like characteristics. Although

design of stronger binding PPI inhibitors with sufficient water solubility has been a significant challenge to drug design due to the largely hydrophobic nature of the PPI targets, these novel and more hydrophilic 2-aminoquinoline compounds are the strongest binding small-molecule ligands for an SH3 domain discovered to date. These promising results demonstrate the potential of extended 2-aminoquinoline compounds as more effective and drug-like ligands for the Tec SH3 domain, and also give important information about the nature of the binding interaction which assists the design of even more effective ligands.

3 Synthesis of 6-position biarylpiperidine substituted 2-aminoquinolines

3.1 Introduction

While the range of simple benzylpiperidine-type ligands were designed to investigate and improve the binding interactions with the Tec SH3 domain, they were not anticipated to make any substantial additional contacts with the protein surface due to their similar size and scaffold. It was however envisaged that extending the structure further may increase contacts with the protein surface and result in a much stronger binding ligand.

The proposal that further interactions with the Tec SH3 domain binding surface can be accessed by larger 6-position substituents was supported by previous work into phenoxy-extended quinoline ligands.[57] The binding affinity of biphenyl-extended compounds (**16a** and **16b**, Figure 66) with the Tec SH3 domain had previously been investigated using [^{1}H,^{15}N]-HSQC chemical shift perturbation experiments.[57] The assay results were inconsistent with those obtained for other 6-position extended 2-aminoquinoline derivatives, and indicated that the biphenyl ligands could favourably interact with the protein binding surface through either the key 2-aminoquinoline structure or through the bulky 6-position substituent, but not both simultaneously. The K_d values measured also indicated that the binding affinity of these ligands with the Tec SH3 domain may be comparable to the strongest identified 2-aminoquinoline ligands, despite the irregular binding interactions. Given the success of various piperidine-extended ligands binding to the SH3 domain, it was proposed that 2-aminoquinolines with 6-position biphenylmethylpiperidine substituents (**113a** and **113b**, Figure 66) may be able to access both binding interactions simultaneously and therefore result in stronger binding to the Tec SH3 domain.

The two isomers of **113**, with different substitution position of the second phenyl group, were each targeted so the optimal contact of the substituent could be found, and potentially find a ligand shape which will best access all of the identified favourable binding interactions and avoid the previously observed irregular binding behaviour of the phenoxy ligands.

A study of molecular substructures which enhance the binding interactions of small molecules with protein targets, including PPI interactions, identified that biphenyl structures were abundantly represented amongst the active ligands investigated.[89] It was hypothesised that biphenyl structures may have improved binding interactions with a protein target in many instances, compared to a phenyl or other aromatic structure, due to the size and flexibility which could enable it to favourably interact with a larger region of protein surface. The addition of phenyl and other bulky lipophilic groups has proved to be an effective strategy for improving the binding affinity of the 2-aminoquinoline ligands with the Tec SH3 domain

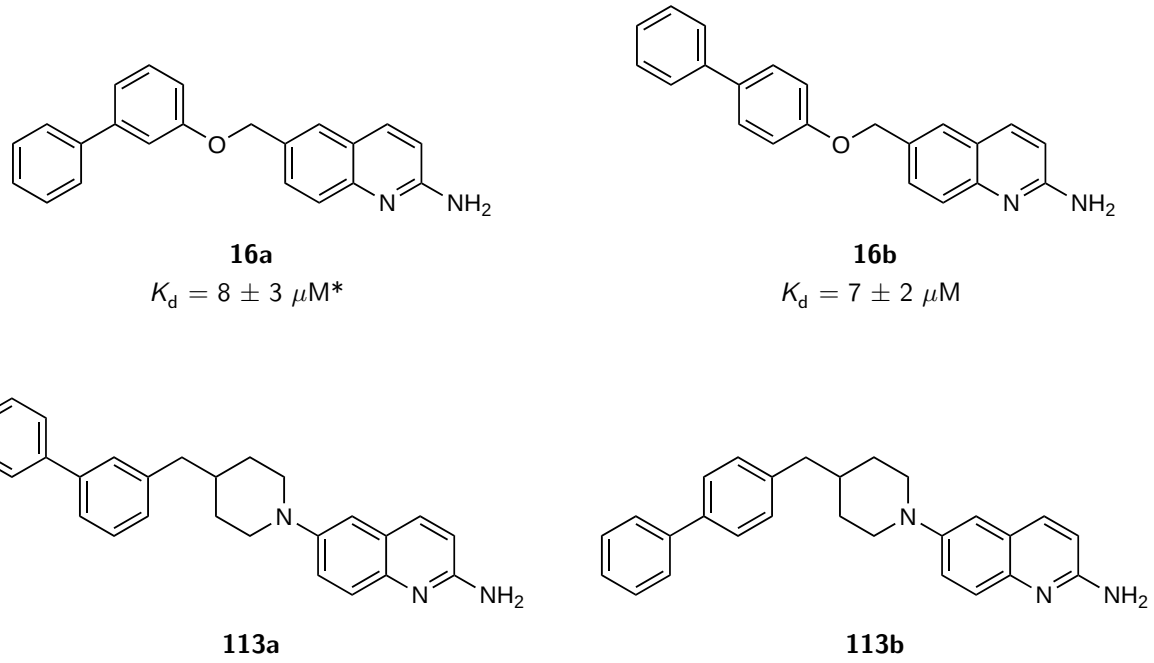


Figure 66: Comparison of biphenyl ligands **16a** and **16b** made previously,[57] and target biphenyl ligands **113a** and **113b**. The previously investigated ligands **16a** and **16b** exhibited irregular binding affinity in the chemical shift perturbation assays, and revised K_d values are shown. ***16a** was assayed as a 7:1 mixture with **16b**.

previously, but while this has identified additional hydrophobic binding interactions it has also resulted in a largely aromatic and hydrophobic scaffold. One of the significant challenges of inhibiting PPIs with small molecules is the typically flat and hydrophobic surfaces being targeted, which leads to development of similarly hydrophobic small-molecule ligands which have issues with water solubility and less drug-like properties. The proposed biphenyl-extended ligands (**113a** and **113b**) were not expected to be very soluble in water and therefore a wider range of biaryl-extended target compounds were proposed, with the second phenyl ring replaced with heteroaromatic rings predicted to improve water solubility (Figure 67).

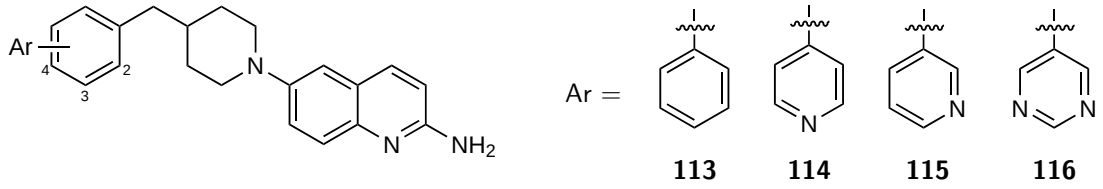


Figure 67: Target biaryl extended 2-aminoquinoline ligands.

In addition to reducing the hydrophobicity of the structure, the heteroaromatic rings have lower electron density compared to the biphenyl compounds which may impact the binding interaction with the Tec SH3 domain. Despite the differences, if biphenyl-extended ligands can be targeted with heteroaromatic rings without compromising the favourable binding interactions of benzene rings, then this strategy could be more widely applied in PPI inhibitor development in cases where largely aromatic scaffolds result in unfavourable water solubility.

3.2 Synthesis of 2-aminoquinolines with 6-position biaryl substituents

3.2.1 General synthetic pathway

The method of successive Buchwald-Hartwig coupling reactions was used effectively to synthesise a large range of 6-position extended 2-aminoquinoline derivatives reported in the previous chapter, and therefore it was expected the same method could be used to synthesise the larger biaryl-extended piperidine structures **113**-**116** from the quinoline intermediate **24** and an appropriate benzylpiperidine.

The synthesis of biaryl structures has been widely reported in the literature previously, utilising palladium-catalysed coupling of an aryl halide with another aryl reagent to form the new carbon-carbon bond. Common methods for synthesis of biaryl compounds include Suzuki, Stille, or Hiyama reactions which each use different types of aryl reagents (Figure 68), and each method has demonstrated versatility and been utilised to make a wide range of biaryl compounds. The Suzuki method, however, has several advantages which made it the preferred method to synthesise the biaryl-extended piperidine targets. The commercial availability of a wider range of arylboronic acid derivatives and the low toxicity of these reagents, particularly compared to the organostannanes, meant the Suzuki reaction was the preferable method for synthesis of biaryl compounds.

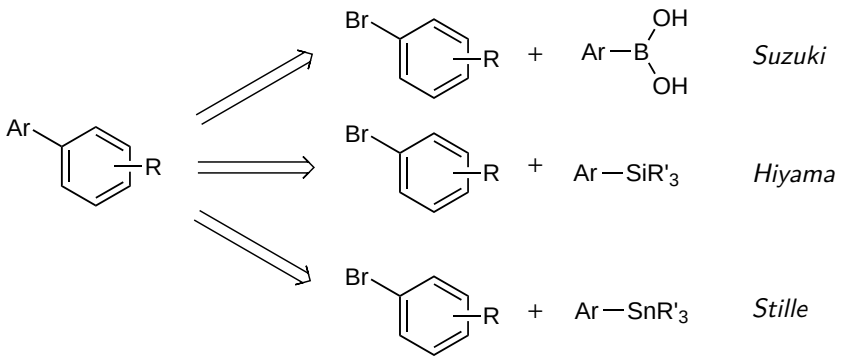


Figure 68: Common palladium-catalysed methods used to synthesise biaryl compounds from aryl bromide reagents.

Given that the bromo-substituted benzylpiperidines **45k-m** had been effectively synthesised already (see Scheme 21, Table 6), it was proposed these could be a suitable aryl halide intermediate. Ideally, it is desired that an efficient pathway with the lowest number of intermediates required to obtain the full range of derivatised compounds would be feasible, for example a process involving coupling of the bromo-substituted benzylpiperidine reagents to the quinoline with the aryl-couplings as the final step (Pathway 1, Figure 69). The competing reactivity of the aryl halides in the intermediate compounds makes this infeasible, however,

as a range of coupling reactions would be expected to occur. Therefore, the formation of the biaryl group via carbon-carbon bond formation must necessarily occur before the Buchwald-Hartwig aminations (Pathway 2), and so a synthesis of the novel compounds **117**-**120** must be developed.

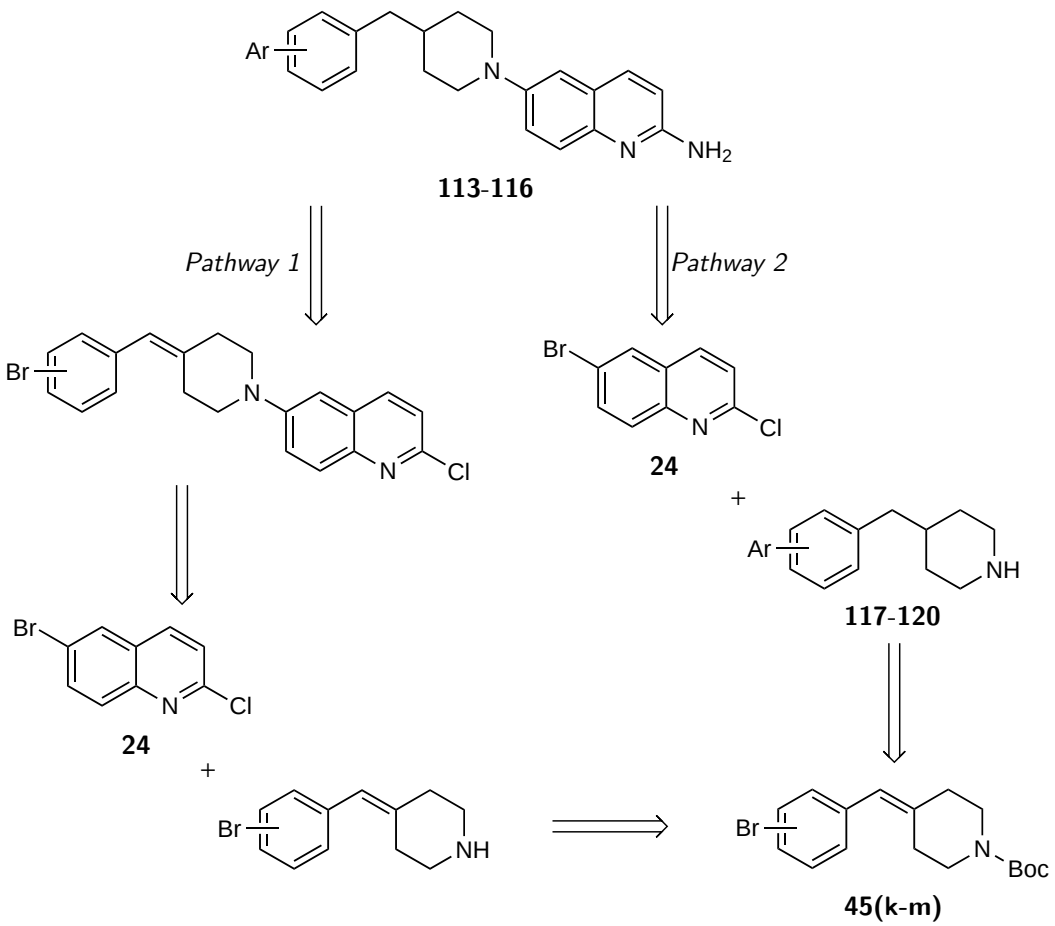
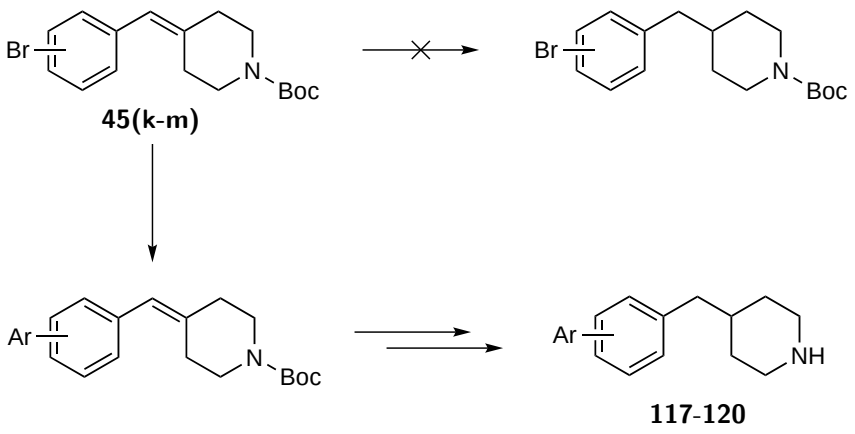


Figure 69: Proposed retrosynthesis of 2-aminoquinoline derivatives with 6-position biaryl-extended substituents.

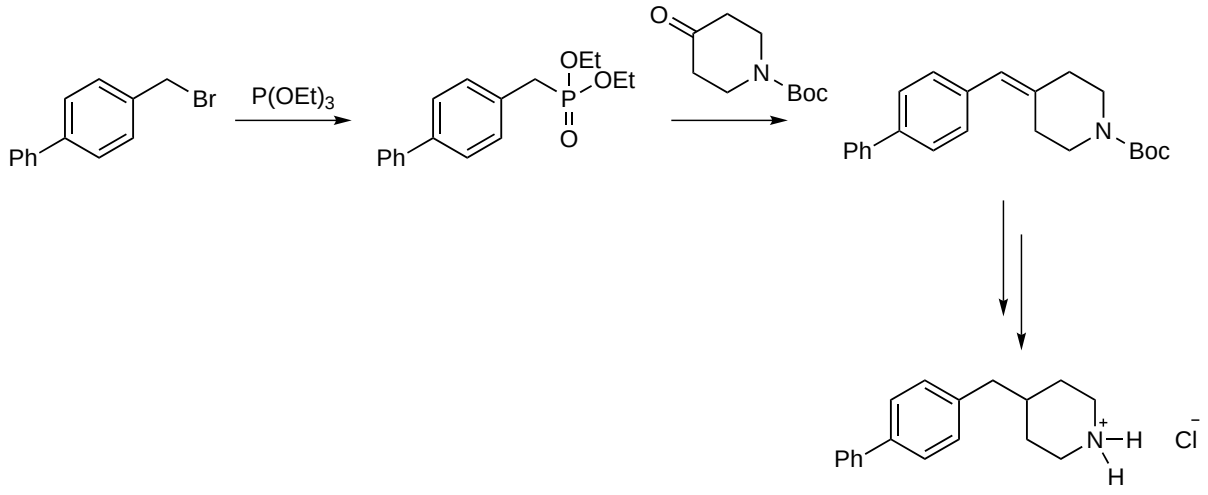
To synthesise the required piperidines (**117**-**120**), a similar synthetic procedure was envisaged to the extended range of substituted benzylpiperidines made previously. As previously demonstrated, hydrogenation of the aryl halide intermediates results in the hydrogenolysis of the aryl halide bond, therefore the hydrogenation of the alkene must occur after formation of the biaryl structure. The proposed synthetic pathway to minimise loss of yield by side-reactions therefore involves coupling of the second aromatic ring via a carbon-carbon bond formation reaction, followed by hydrogenation and deprotection of the Boc-protecting group analogous to synthesis of benzylpiperidines previously (Scheme 80).



Scheme 80: Proposed synthesis of novel biaryl-substituted piperidines **117-120**.

3.2.2 Synthesis of biphenyl/biaryl substituted 4-methylpiperidines

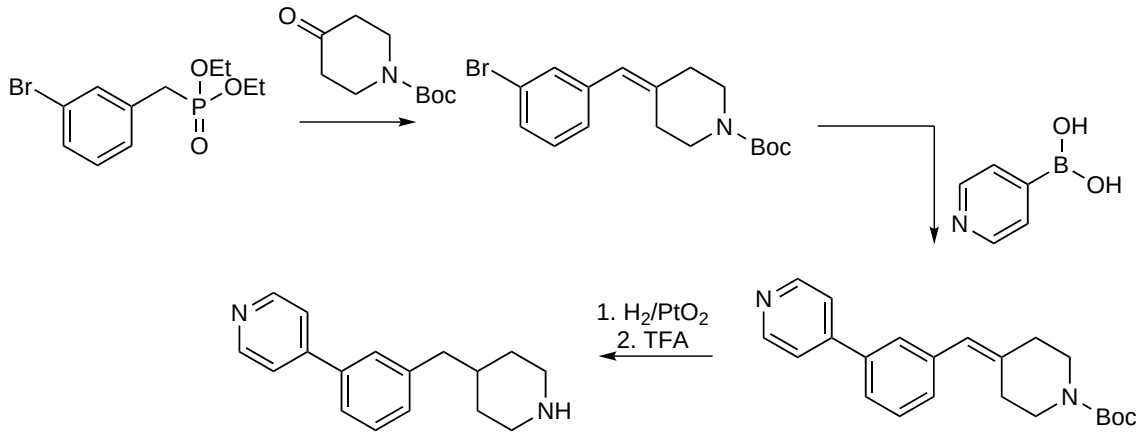
There were very few previous syntheses reported for the proposed range of biaryl-extended piperidine compounds targets. One alternate synthesis of a biphenyl compound **117b** had been reported previously in a patent, from biphenylbromide reagents using a Horner-Emmons reaction as the key carbon bond forming step (Scheme 81),[62] very similar to the benzylpiperidines previously synthesised (see Schemes 10, 12). This method would not be considered ideal for this project because a large number of aryl-substituted benzyl bromides and corresponding phosphonates would need to be synthesised, whereas the proposed method using the previously synthesised bromo-substituted piperidines **45(k-m)** reduces the number of intermediates required to synthesise the full range of target compounds.



Scheme 81: Reported synthesis for a biphenyl-extended piperidine derivative. Yield and spectroscopic data for novel compounds were not reported, and products were not purified.[62]

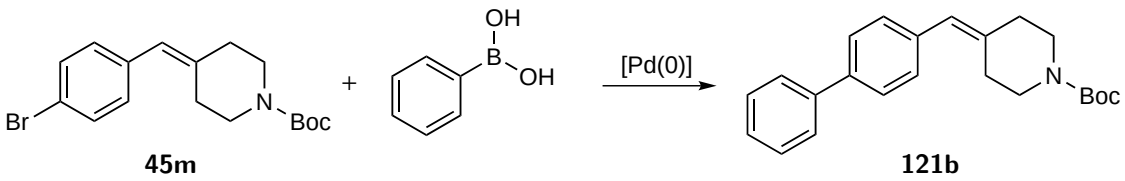
Of the heteroaromatic-extended piperidine targets, only 4-pyridinyl-substituted derivatives had a previously reported synthesis.[90] These compounds were also only reported in a patent,

and the synthesis utilised a Suzuki reaction with 4-pyridinylboronic acid to make the biaryl structure, similar to the method proposed above (Scheme 82). More broadly, Suzuki reactions have been used to make a range of biaryl compounds from arylboronic acids and aryl bromides with a wide range of reported reaction conditions. For the proposed targets, coupling of phenyl, pyridinyl, and pyrimidinyl boronic acid derivatives is required, and of these the heteroaromatic boronic acids were less utilised in literature syntheses than phenylboronic acid.



Scheme 82: Reported synthesis for a biaryl-extended piperidine derivative. Overall yield and spectroscopic data for novel compounds was not reported.[90]

From the literature methods, several reaction conditions that achieved successful results for coupling of phenylboronic acid with aryl bromides were tested in the attempted coupling of **45m** and phenylboronic acid (Scheme 83, Table 23).[3,91,92] Under most of the tested reaction conditions large quantities of reagents were recovered and minimal to zero conversion to the desired product **121b** was observed. In only one case, using a sealed tube reaction, was complete conversion to the product observed, and the product in this case was purified.



Scheme 83: Attempted syntheses of biphenyl-extended piperidine **121b** via Suzuki reaction. For conditions and results see Table 23.

Comparison of the NMR spectra of the bromo-substituted reagent and the phenyl-coupled product demonstrated that the desired biphenyl product had been obtained. The appearance and integration of the aromatic signals in the ^{1}H NMR spectrum was consistent with an additional phenyl group (Figure 70), and 2D NMR experiments were used to conclusively demonstrate that the coupling reaction had occurred at the desired position. HRMS analysis of the purified material was consistent with the biphenyl product **121b** in contrast to the

Table 23: Exploration of Suzuki coupling conditions for synthesis of a biphenyl-extended piperidine derivative (**121b**) based upon literature Suzuki conditions. *Determined from ^{1}H NMR spectrum of crude reaction mixture.

Pd catalyst/ligand	Solvent	Base	Method	Ratio 45m:121b*	Yield (%)
$Pd(PPh_3)_4$	DMF	K_2CO_3	80°C[3]	9:1	
$Pd(OAc)_2/PPh_3$	toluene	K_2CO_3	reflux	1:0	
$Pd(OAc)_2/PPh_3$	toluene	K_2CO_3	100°C, sealed	0:1	73
$Pd(PPh_3)_4$	toluene	K_2CO_3	80°C[91]	1:0	
$Pd(PPh_3)_4$	toluene	K_2CO_3	80°C, sealed[91]	3:1	
$Pd(OAc)_2$	H_2O/DMF	Na_2CO_3	35°C[92]	1:0	

distinctive isotope peaks observed for the bromo-substituted reagent **45m**. The signals corresponding to the atoms of the piperidine ring appeared very similar to those of the reagent, showing that the piperidine ring of the coupled product is also substantially planarised and that interconversion between ring conformations is slow on the NMR timescale.

For each of the other reaction conditions tested a mixture of product and recovered reagent was obtained. These mixtures were not purified, and the approximate ratio of product and recovered reagent **45m** could be determined using ^{1}H NMR spectroscopy of the crude reaction mixture. While some aromatic and piperidinyl signals were coincident or overlapped in the ^{1}H NMR spectrum, the alkene signals were distinct and therefore the integration of these signals (at 6.277 ppm for the reagent, and 6.384 ppm for the product) gave the relative molar ratio of components in the reaction mixture.

The same reaction conditions were used to achieve the synthesis of **121a** with a good yield (Table 24). The formation of the 3-position phenyl-substituted derivative resulted in an downfield shift of the alkene signal in the ^{1}H NMR spectrum similar to **121b**. The shifts of the aromatic NMR signals, as well as HRMS and 2D NMR data confirmed the structures of the isolated product.

The synthesis of **122b** from 4-pyridinylboronic acid and **45l** was attempted using the same reaction conditions used for the synthesis of **121b**, however this did not result in synthesis of the desired product and only reagents were recovered from the reaction mixture (Scheme 84).

Given the relative hydrophilicity of the heteroaromatic boronic acids it was expected that poor solubility of the reagents in toluene was potentially an issue. The Suzuki reaction is tolerant of a wide range of solvents, and so the same reaction was attempted using a 1:1 mixture of toluene and ethanol which was expected to increase solubility of the reagent especially at the elevated reaction temperature. The reaction under these conditions resulted

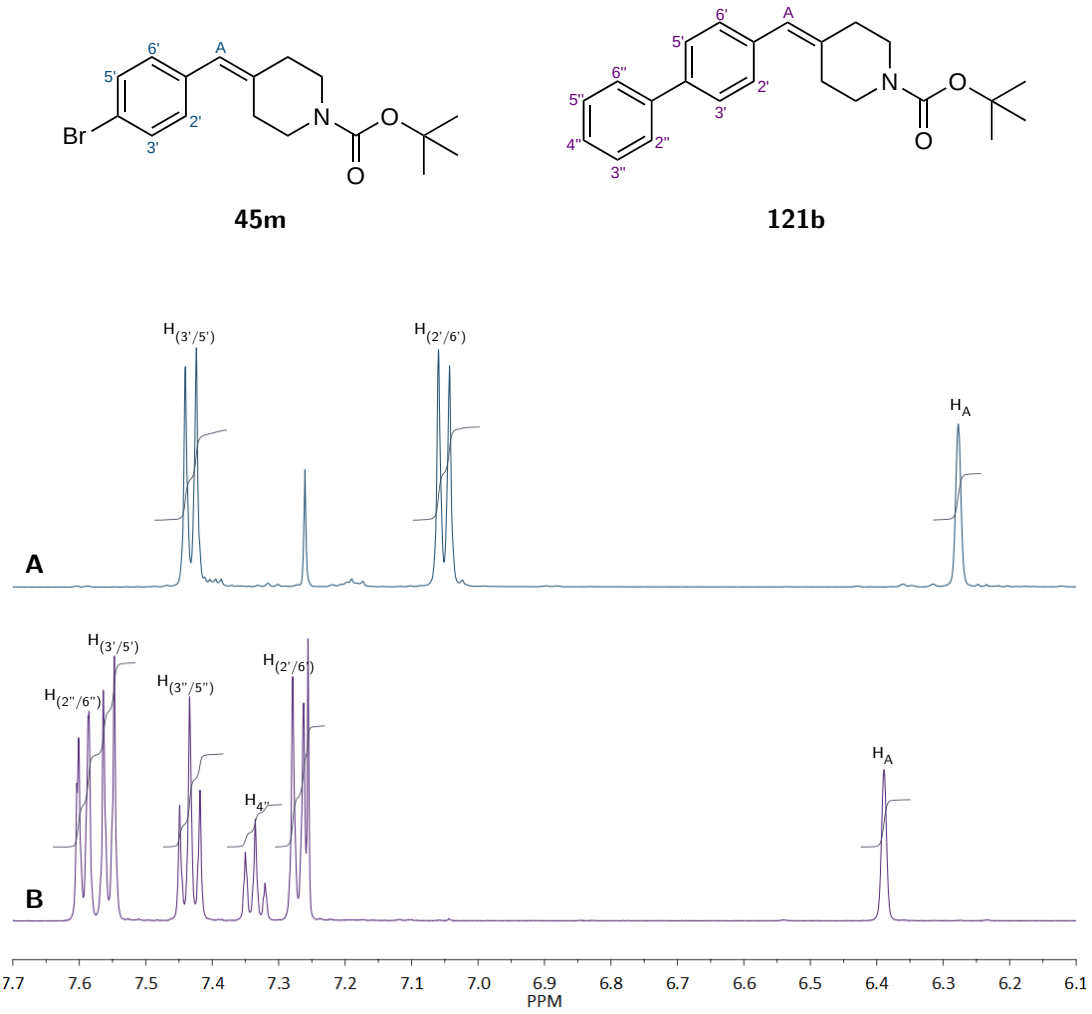
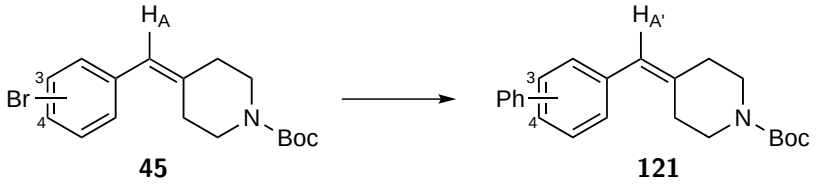
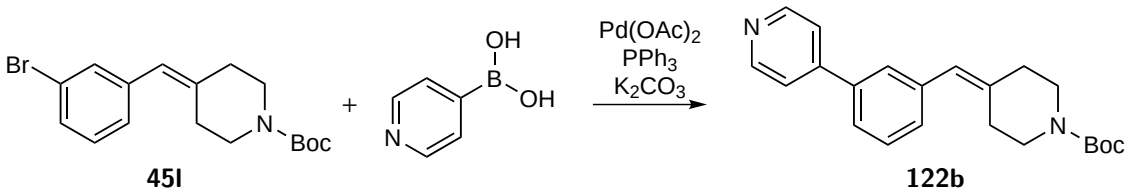


Figure 70: Comparison of signals in the ^{1}H NMR spectra of Boc-protected 4-piperidines before and after Suzuki coupling, demonstrating successful synthesis of the biphenyl group. A: Downfield region of ^{1}H NMR spectrum for bromo-substituted reagent **45m**, and B: same region of ^{1}H NMR spectrum for biphenyl-substituted product **121b**.

Table 24: Yields of biphenyl-extended piperidine derivatives **121** derivatives from Suzuki reactions.



Reagent	Br position	δ_H H_A (ppm)	Product	δ_H $H_{A'}$ (ppm)	Yield (%)
45l:	3	6.289	**121a**:	6.422	81
45m:	4	6.277	**121b**:	6.384	73



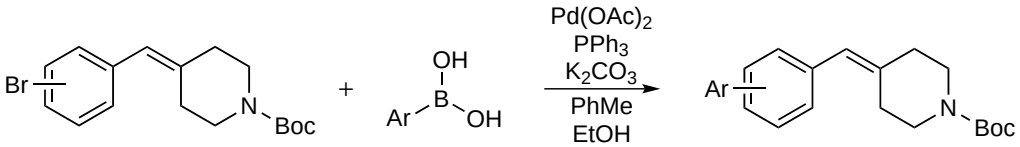
45l **122b**

Solvent (Ratio)	Yield 122b (%)
toluene	0
toluene/ethanol (1:1)	100

Scheme 84: Attempted syntheses of biaryl-extended piperidine **122b** via Suzuki reaction.

in successful synthesis of the desired product **122b**, as clearly demonstrated by the HRMS data of the product and the 2D NMR spectra. A longer reaction time was required for complete conversion, and with purification a quantitative yield of **122b** was achieved.

Using the same conditions, the other heterocyclic compounds **122-124** were successfully synthesised and isolated generally with high yields (Scheme 85, Table 25).



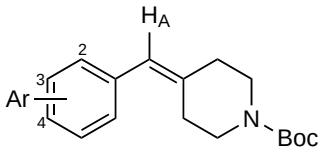
45 **122-124**
51-100%

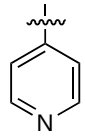
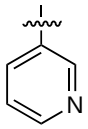
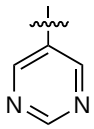
Scheme 85: Synthesis of biaryl-extended piperidine derivatives via Suzuki reaction. For Ar groups used, see Table 25.

Successful coupling of the 2-substituted biaryl derivatives (**122a**, **123a** and **124a**) resulted in an upfield shift of the alkene ^{1}H NMR signal, whereas for the 3- and 4-position substituted biaryls the alkene signal was shifted downfield compared to the alkene hydrogen signal of the aryl bromide reagents. The successful coupling of the heteroaromatic ring was demonstrated by the increased number of signals in the ^{1}H and ^{13}C NMR spectra compared to the bromo-substituted reagents, and HMBC correlations of the aromatic ring signals were used to conclusively determine that the coupling had occurred in the desired position (see example in Figure 71).

Similar to all other Boc-protected piperidine derivatives, the broadness in the piperidine signals in the ^{1}H and ^{13}C NMR spectra was consistent with the proposed substantially planarised ring structure and slow rotation of the Boc-protecting group on the NMR timescale. HSQC experiments were required to determine the chemical shifts of the broadest ^{13}C NMR signals, which corresponded to carbon atoms adjacent to the Boc-protected nitrogen atom. HRMS data was also collected and in every case the observed mass confirmed the loss of the bromine

Table 25: Yields of biaryl-extended piperidine derivatives from Suzuki reactions.



Ar =	Compound	Ar position	δ_H H_A (ppm)	Yield (%)
	**122a**:	2	6.164	62
	122b:	3	6.432	100
	122c:	4	6.396	100
	**123a**:	2	6.164	57
	123b:	3	6.426	91
	123c:	4	6.396	51
	**124a**:	2	6.167	86
	124b:	3	6.428	87
	124c:	4	6.406	92

atom and was consistent with the expected products.

The following steps were simple hydrogenation and removal of the Boc-protecting group to give the target piperidine compounds, and the same conditions used for the simpler benzylpiperidine synthesis were utilised (Scheme 86). Reduction of the alkene products by hydrogenation took a significantly longer time compared to the simpler benzylidenepiperidines prepared previously (typically 16 hr, compared to 2 hr for most derivatives of **45**), but full conversion to the reduced product was achieved in each case and the yield was typically quantitative (Table 26).

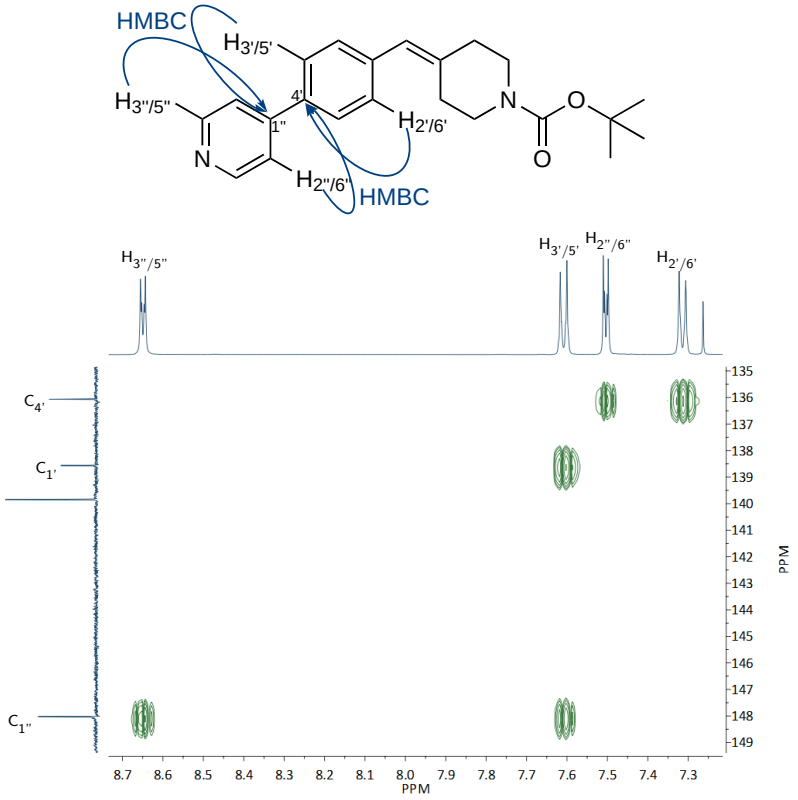
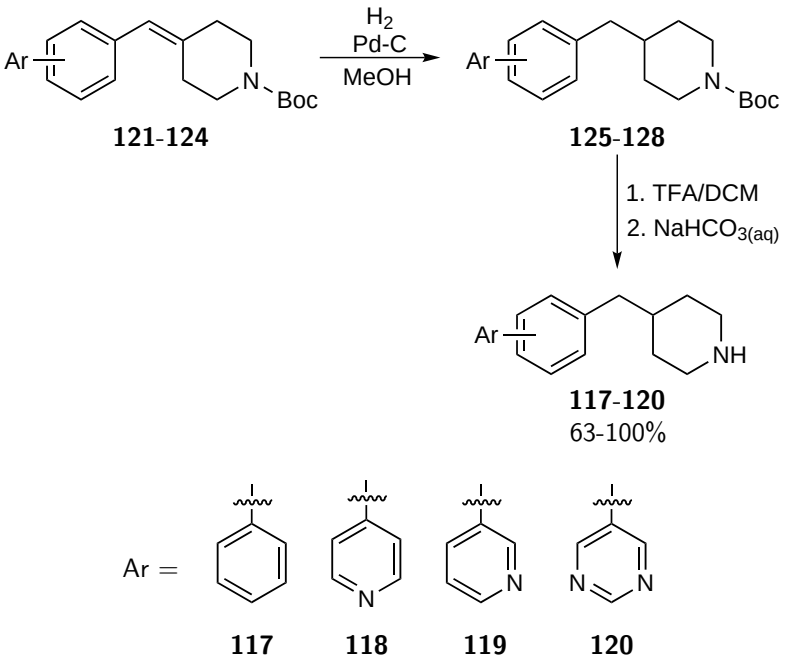


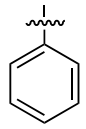
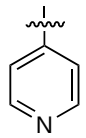
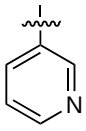
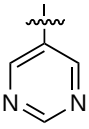
Figure 71: HMBC correlations between aromatic rings demonstrating successful Suzuki coupling to make biaryl-extended structure. Example spectra shown are for the novel compound **122c**.



Scheme 86: Synthesis of biaryl-extended piperidine derivatives (**117**-**120**) via hydrogenation and Boc-deprotection reactions.

Aside from the required length of the reaction, the results of the reaction were very similar to the synthesis of the simpler benzylpiperidine derivatives **48** from **45** previously. The changes in the ^{1}H NMR spectrum demonstrated a change in conformation of the piperidine ring, showing

Table 26: Yields of biaryl-extended 4-piperidine derivatives from alkenes over two steps.

Ar group/ position			δ_H H_A (ppm)	δ_H $H_{2/6}$ (ppm)		δ_H $H_{2/6}$ (ppm)	2-Step Overall Yield (%)
	3	**125a:**	2.60	2.64/4.08	**117a:**	2.70/3.26	
	4	**125b:**	2.57	2.65/4.08	**117b:**	2.65/3.18	99
	2	**126a:**	2.55	2.51/3.97	**118a:**	2.56/3.13	100
	3	**126b:**	2.62	2.65/4.09	**118b:**	2.79/3.35	63
	4	**126c:**	2.60	2.65/4.09	**118c:**	2.74/3.29	74
	2	**127a:**	2.54	2.51/3.96	**119a:**	2.59/3.16	92
	3	**127b:**	2.62	2.65/4.09	**119b:**	2.79/3.34	100
	4	**127c:**	2.59	2.66/4.09	**119c:**	2.71/3.26	98
	2	**128a:**	2.54	2.52/3.99	**120a:**	2.53/3.09	73
	3	**128b:**	2.64	2.66/4.10	**120b:**	2.67/3.21	65
	4	**128c:**	2.62	2.66/4.10	**120c:**	2.74/3.28	82

distinct axial and equatorial hydrogen signals indicative of a more chair-like conformation of the ring, and the overall appearance of the ^{1}H NMR spectrum was analogous to the simpler benzylpiperidine derivatives observed previously (Figure 72). The signals corresponding to atoms adjacent to the Boc-protected nitrogen atom were still broadened in the ^{1}H and ^{13}C NMR spectra as due to the protecting group which exhibits slow rotation on the NMR timescale. An increase in the product mass determined by HRMS also corresponded to addition of two hydrogen atoms in each case.

The removal of the Boc-protecting group catalysed by TFA proceeded as expected to give the products **117**-**120**, again with results comparable to the simpler substituted benzylpiperidines (Table 26). The spectroscopic results were consistent with isolation of the desired piperidine compounds, most notably the distinct absence of the *tert*-butoxy signals in the NMR spectra and the corresponding mass loss as determined by HRMS analysis of the products. The characteristic sharper piperidine signals in the ^{1}H and ^{13}C NMR spectra were also observed without the impact of slow rotation of the Boc-protecting group. Aside from the difference in appearance observed for the ^{1}H NMR signals, an upfield shift for the equatorial hydrogen atoms adjacent to the piperidine nitrogen was observed compared to the starting material, due to the loss of the promixate carbonyl in the protecting group which caused the equatorial

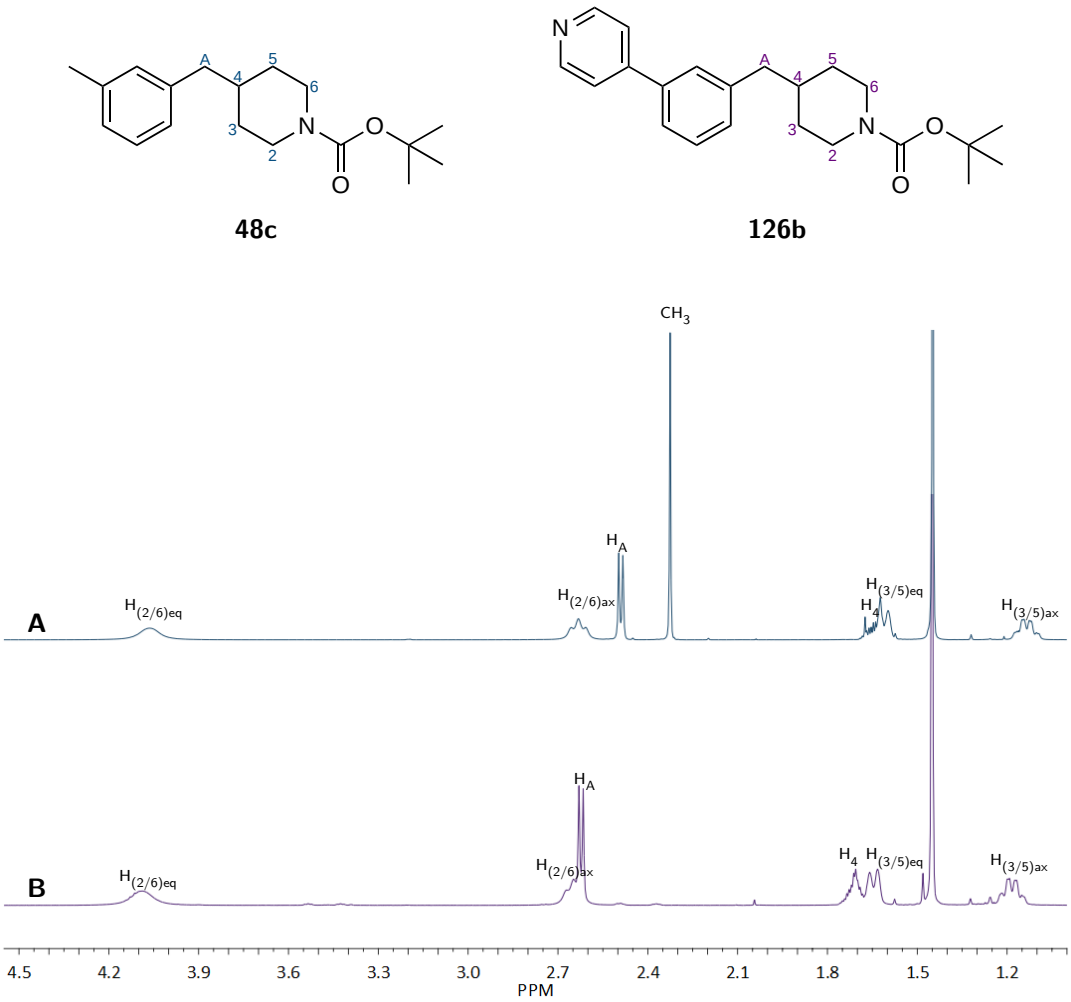


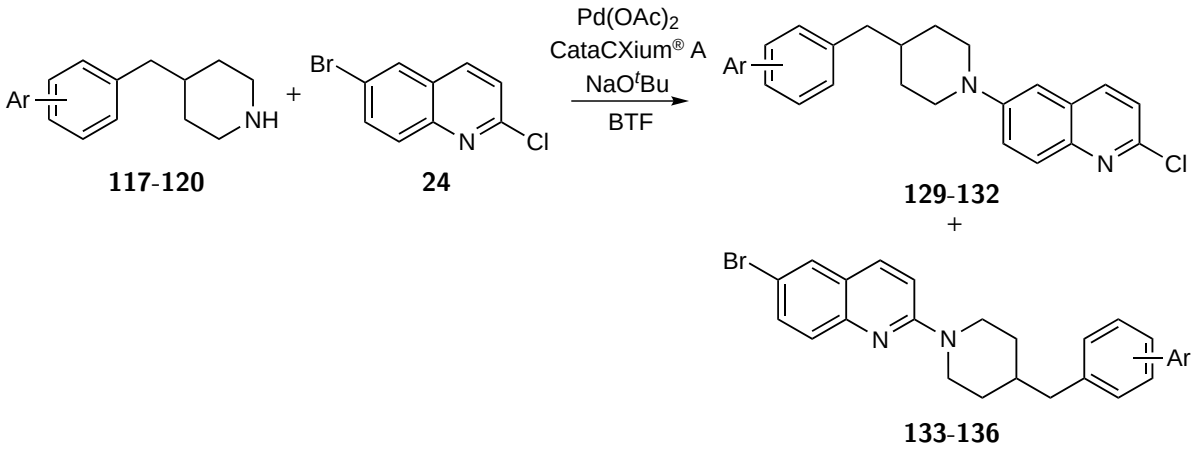
Figure 72: Comparison of piperidine ring signals in the ^{1}H NMR spectra of Boc-protected 4-piperidines, showing similar characteristics and indicating analogous shape of structures. A: Upfield region of ^{1}H NMR spectrum for simple benzylpiperidine **48c**, and B: same region of ^{1}H NMR spectrum for biaryl-extended piperidine **126b**.

hydrogen atoms to be deshielded by anisotropy. The yields isolated from this method ranged considerably from moderate to high yields, and it is expected that the variance is due to the work-up procedure which involves a liquid-liquid extraction and therefore results in lower yields of some derivatives. Broadly, this method was effective for the range of derivatives which were the target of this work.

3.2.3 Synthesis of 2-aminoquinolines via Buchwald-Hartwig aminations

The coupling of the piperidines **117**-**120** to the 6-position of the quinoline compound **24** was attempted using the same Buchwald-Hartwig amination conditions used for the simpler benzylpiperidine derivatives in the previous chapter, as a sealed-tube reaction (Scheme 87). From the previous work, it was expected that under the palladium-catalysed reaction conditions the 6-position substituted quinoline derivatives **129**-**132** would be the major or exclusive

products in each case, although some side-reactions could potentially occur. In particular, it was previously found that coupling at the 2-position of the quinoline could potentially occur which would give the unwanted side-products **133**-**136**.



Scheme 87: Buchwald-Hartwig amination for synthesis of biaryl extended 2-chloroquinoline derivatives.

The presence and relative quantities of these major products could be observed by ^{1}H NMR analysis of the crude mixture without purification due to the distinctive chemical shift differences: the quinoline hydrogen signals adjacent to the piperidine substituent had a significant upfield shift compared to the reagent, appearing near 7 ppm, and therefore by measuring the coupling constant of the upfield doublet signal (coupling constants were typically $^{3}J_{3,4} = 9$ Hz for H_3, or $^{4}J_{5,7} \approx 2.5$ Hz for H_5 signal) the regioselectivity of the reaction could be determined (Figure 73). Significant differences were also observed for the piperidine ring signals, with the 2-position substituted side-products showing a more downfield shift for the equatorial $H_{(2'/6')}$ signals due to the quinoline nitrogen adjacent to the piperidine substituent.

From the experiments, it was found that the Buchwald-Hartwig aminations generally yielded moderate yields of the desired products **129**-**132**, with small amounts of the 2-position coupled products **133**-**136** observed for a minority of derivatives (Table 27). For only one attempted reaction, the coupling of **119c** with **24**, was a sufficient amount of the side-product **135c** produced to enable isolation. Unlike the simpler benzylpiperidine coupling reactions attempted previously, there were no derivatives for which only 2-position substitution was observed. The results demonstrate that further exploration of the reaction conditions was not required in this case to adapt for the coupling of significantly larger piperidine derivatives.

The major products were isolated and in each case the spectroscopic results were used to confirm the desired product has been successfully synthesised. Coupling of the substituent at the 6-position of the quinoline was indicated by distinctive shifts differences in the ^{1}H and ^{13}C NMR spectra as noted previously, in particular the large upfield shift of the H_5 doublet signal due to the adjacent piperidine substituent. The C_6 signal appears far downfield in the ^{13}C NMR spectra of the products due to the electronegative nitrogen substituent, and

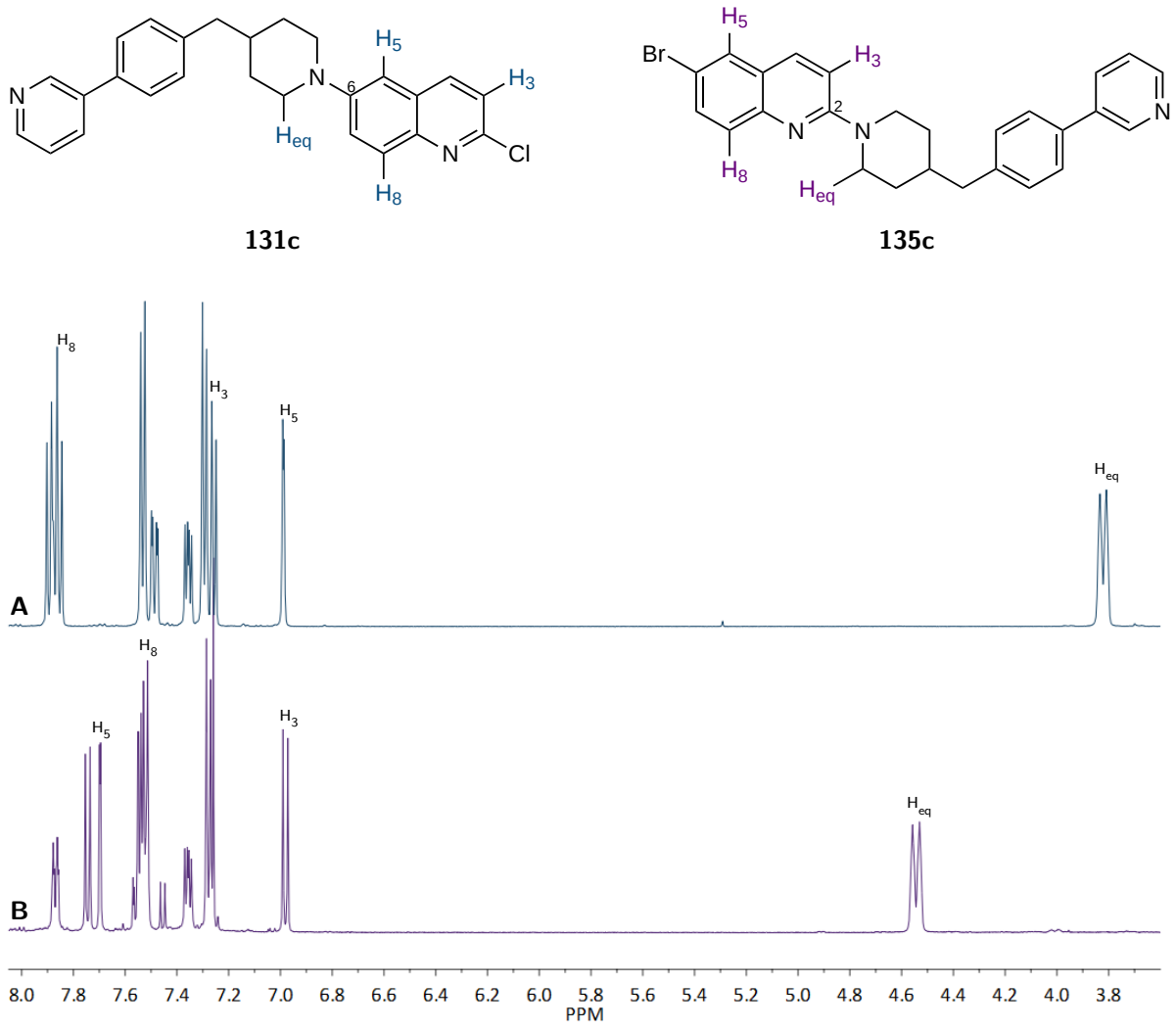
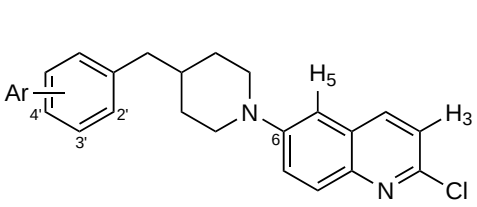


Figure 73: Comparison of ^{1}H NMR spectra of Buchwald-Hartwig amination products, showing distinctive signal and chemical shift differences. A: ^{1}H NMR spectrum of target 6-position substituted product **131c**, and B: ^{1}H NMR spectrum of 2-position substituted side-product **135c**.

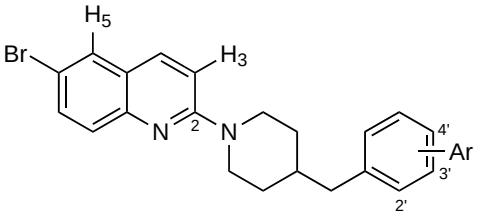
HMBC experiments showed correlations between this C_6 signal of the quinoline ring and the piperidine ring hydrogen signals further demonstrating the successful coupling at only the 6-position (Figure 74A). HRMS data showed distinctive peaks for the isolated compounds, consistent with the expected isotopic abundances due to the 2-position chloro-substituent of the quinoline product.

The isolated 2-position substituted product **135c** showed contrasting chemical shift differences in the NMR spectra due to the alternate position of the electron-donating piperidine substituent on the quinoline ring (see Figure 73B). In the ^{1}H NMR spectrum, an upfield shift of the H_3 doublet signal with a larger coupling constant, instead of an upfield shift of the H_5 signal, was observed. The comparatively downfield shift of the equatorial $H_{(2'/6')}$ signals is also consistent with substitution adjacent to the quinoline nitrogen atom. The C_2 signal in the ^{13}C NMR spectrum was the most downfield signal in the spectra of either **131c** or **135c** due to the adjacent quinoline nitrogen and the piperidine substituent, and for **135c** the HMBC

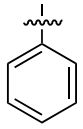
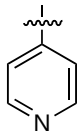
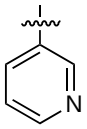
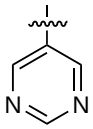
Table 27: Results of Buchwald-Hartwig amination reactions for biaryl-extended piperidine derivatives. Chemical shifts for ^{1}H NMR signals are reported in units of ppm, and coupling constants are reported in Hz.



129-132



133-136

Ar group/ position			δ_H H_5 (^4J)	δ_H H_3 (^3J)	Yield (%)		δ_H H_3 (^3J)
	3'	**129a**:	6.98 (1.8)	7.25 (8.6)	42		
	4'	**129b**:	6.97 (1.8)	7.24[b]	55		
	2'	**130a**:	6.93 (2.5)	7.25[b]	67		
	3'	**130b**:	6.98 (2.0)	7.25[b]	60	**134b**:	7.01[a] (9.5)
	4'	**130c**:	6.99 (2.6)	7.26 (8.6)	56		
	2'	**131a**:	6.92 (2.7)	7.25 (8.6)	33		
	3'	**131b**:	6.98 (2.6)	7.24[b]	56		
	4'	**131c**:	6.99 (2.6)	7.26 (8.6)	26	**135c**:	6.98 (9.2)
	2'	**132a**:	6.92 (2.6)	7.24[b]	46		
	3'	**132b**:	6.98 (2.6)	7.25 (8.7)	60	**136b**:	6.98[a] (9.1)
	4'	**132c**:	6.99 (2.6)	7.26 (8.6)	36		

[a] Identified from NMR data of crude mixture, not isolated. [b] Peak overlapped, shift identified using 2D NMR experiments.

experiment showed correlations between the C_2 signal and the axial $H_{(2'/6')}$ piperidine signals demonstrating the change in substitution position (Figure 74B). HRMS of the isolated product was consistent with the mass of **135c**, including the characteristic 1:1 isotope peaks due to the bromo-substituent, confirming that the aryl bromide bond (instead of the aryl chloride) was retained under the reaction conditions.

The 2-chloroquinoline derivatives (**129-132**) were converted to the corresponding 2-aminoquinoline target compounds **113-116** by a second palladium-catalysed Buchwald-Hartwig amination (Scheme 88). The results of this method were consistent with those

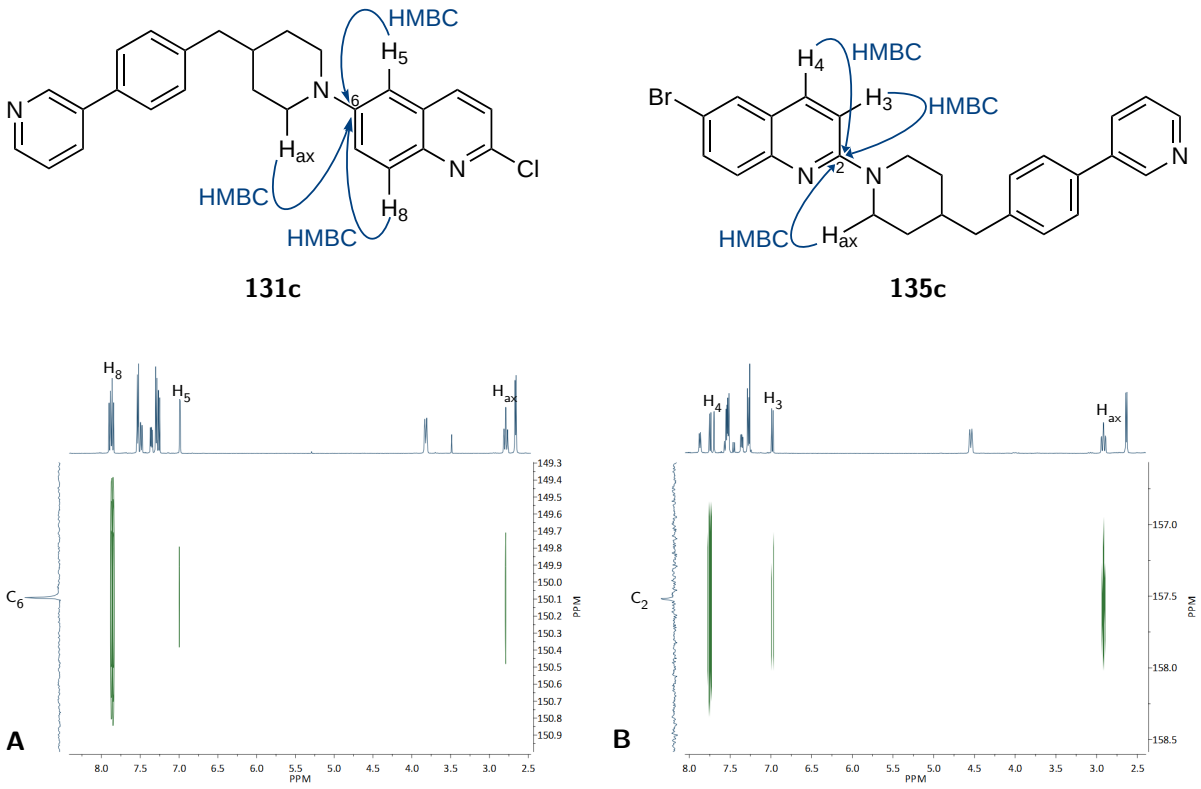
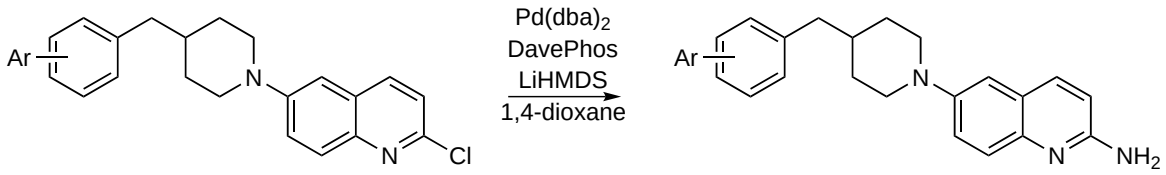


Figure 74: HMBC correlations between piperidine signals and quinoline ring signals showing substitution position of major Buchwald-Hartwig amination products. A; HMBC correlations for C(6) signal of **131c**, and B: HMBC correlations for C_6 signal of **135c**.

obtained previously for synthesis of simpler 2-aminoquinoline derivatives. The yields varied substantially although in most cases moderate conversion to the desired product was achieved, and in each case the target biaryl-extended 2-aminoquionoline derivative was obtained (Table 28).

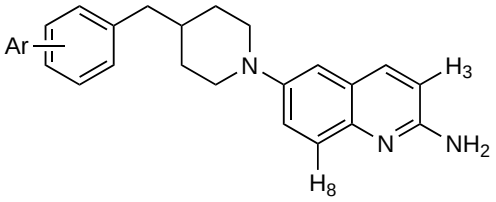


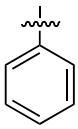
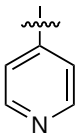
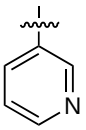
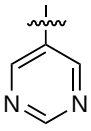
129-132 **113-116**

Scheme 88: Buchwald-Hartwig amination for synthesis of biaryl extended 2-aminoquinoline derivatives.

Success of the reaction was confirmed by spectroscopic analysis, with HRMS analysis showing loss of the chloro-substituent and mass reduction consistent with the target products. From the NMR spectra, upfield shift of the H_3 doublet and C_3 signals compared to the reagent was observed due to the electron-donating amino group, with other signals which are shielded by resonance, including H_8, also showing a smaller upfield shift difference. It was noted in several instances that the quaternary C_{8a} signal for the 2-aminoquinoline compounds was very broad and could not be distinguished from the baseline of the ^{13}C NMR spectrum. The presence of a signal for the C_{8a} atom in these cases was clearly demonstrated using HMBC

Table 28: Results of Buchwald-Hartwig amination reactions for synthesis of biaryl-extended 2-aminoquinoline derivatives.



Ar group/ position			δ_H H_3 (ppm)	δ_H H_8 (ppm)	Yield (%)
	3	**113a**:	6.70	7.58	44
	4	**113b**:	6.67	7.57[a]	54
	2	**114a**:	6.69	7.55	55
	3	**114b**:	6.68	7.58	32
	4	**114c**:	6.69	7.58	54
	2	**115a**:	6.66	7.55	67
	3	**115b**:	6.66	7.56	59
	4	**115c**:	6.67	7.58	63
	2	**116a**:	6.66	7.54	52
	3	**116b**:	6.70	7.58	37
	4	**116c**:	6.70	7.59	47

experiments, as correlations of the H_5, H_7 and H_4 signals to an indistinguishable ^{13}C NMR signal at approximately 141 ppm were observed (for example, see Figure 75A). This chemical shift is consistent with other 2-aminoquinoline derivatives where the broadened C_{8a} signals were more readily observable as a signal in the ^{13}C NMR spectrum (for example, see Figure 75B), and as there was no overlap with other signals the assignment of the C_{8a} signal was unambiguous in each case.

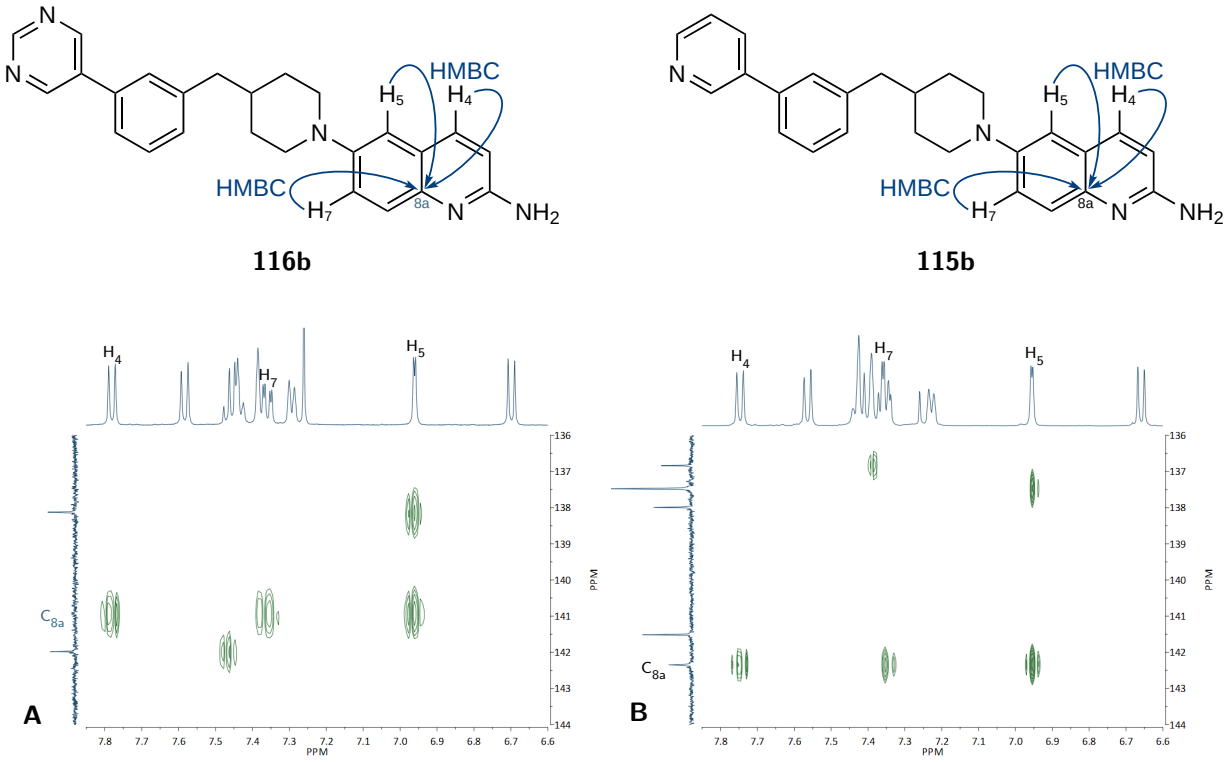
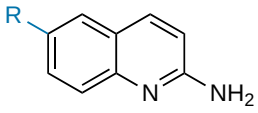


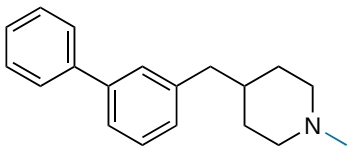
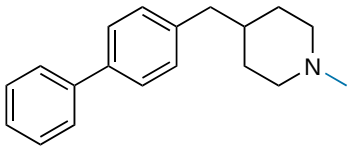
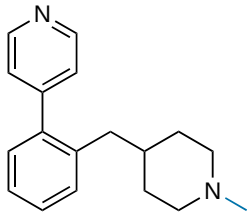
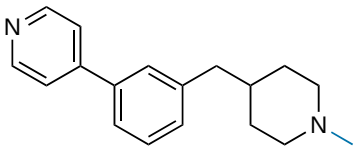
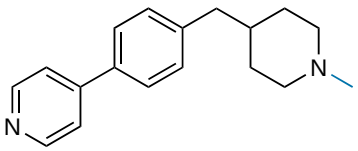
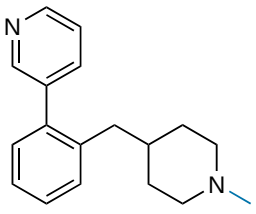
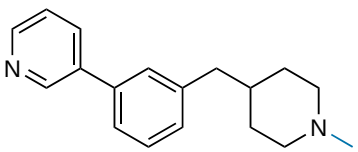
Figure 75: HMBC correlations for C_{8a} signal, which was not always distinctly observed in the ^{13}C NMR spectra of 2-aminoquinoline derivatives. A: HMBC correlations unambiguously denoting position of indistinguishable C_{8a} signal for **116b**, and B: for comparison, HMBC correlations for readily observable C_{8a} signal of **115b**.

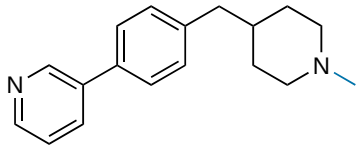
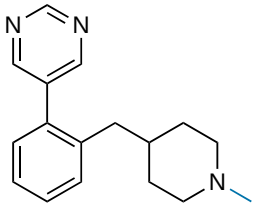
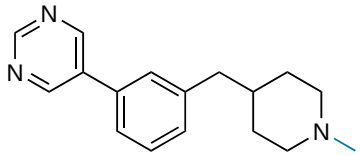
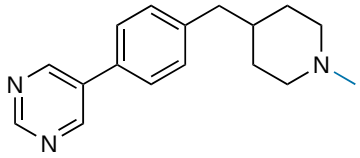
3.3 Binding studies of 6-position biaryl extended 2-aminoquinoline derivatives

The biaryl-extended derivatives **113**-**116** were assayed using the SPR method, as described for the simpler benzylpiperidine derivatives assayed previously. As predicted in the design of these compounds, the biphenyl derivatives (**113**) were too lipophilic and therefore insoluble under the assay conditions. Some of the pyridinyl-extended compounds were also insoluble under the assay conditions, but the strategy of using more hydrophilic heteroaromatic rings was effective, and the majority of the biaryl-extended compounds had improved solubility and therefore the impact of the larger biaryl structure upon the binding affinity could be explored. For the compounds which were soluble under the assay conditions the initial screening method was first used to determine an approximate K_d value. The concentration range for the assay was then adjusted for the replicates in order to generate a binding isotherm and more accurately determine the K_d value (Table 29).

Table 29: Results of SPR assays for 2-aminoquinoline ligands with a 6-position biaryl-extended piperidine substituent.



R =	Compound	Screening K_d (μM)	Assay $K_d \pm$ SD (μM)
	**113a**	*insoluble*	
	**113b**	*insoluble*	
	**114a**	5.4	6 ± 3^a
	**114b**	*insoluble*	
	**114c**	*insoluble*	
	**115a**	13.9	10 ± 4
	**115b**	> 20	

R =	Compound	Screening K_d (μM)	Assay $K_d \pm$ SD (μM)
	**115c**	5.2	7 ± 4^a
	**116a**	9.3	7 ± 1^a
	**116b**	7.9	4.1 ± 0.7^a
	**116c**	3.2	2.4 ± 0.2

[a] Highest concentration data point removed due to precipitation or aggregation of compound under assay conditions.

Compared to the previous lead compound **15**, a comparable or lower K_d value was calculated for each biaryl-extended ligand where the K_d value could be determined using the SPR method. Broadly, this demonstrates that adding the additional aromatic ring does improve the strength of the binding interaction as predicted from the previous experimental results. The reason for the improvement is not evident, however, because a sufficiently strongly binding ligand was not obtained and therefore the 3D structure of a protein-ligand complex could not be determined.

Some limitations of this method were evident in the experimental results, as several of the pyridine compounds did not give consistent binding isotherms and had a large variance in the calculated K_d values. Due to this, the calculated error for **114a**, **115a** and **115b** are significant. Despite the relatively large range in the obtained K_d values, the results still demonstrated that there was a change in the SPR response and therefore indicate that all of these compounds bind to the Tec SH3 protein. The obtained results show that these compounds potentially bind with stronger affinity than the previously identified lead compound **15**, but due to the large error this is not conclusive.

More consistent results were obtained for the other derivatives, and in particular the pyrimidinyl-

extended compounds (**116**). The three derivatives of **116** all demonstrated an improvement in binding affinity compared to the lead compound, and are among the strongest binding small-molecule ligands obtained for the Tec SH3 domain to date. These results indicate that even substantially increasing the size of the 6-position substituent with an additional aromatic ring gives ligands which are readily accommodated in the binding site of the Tec SH3 domain target. The observations that the pyrimidinyl-extended compounds appear to have improved binding affinity while also improving the aqueous solubility is a very promising result for the design of more drug-like and effective small-molecule drugs fo the Tec SH3 domain, which was a key goal of this project. It is apparent from the experimental results for these biaryl-extended 2-aminoquinoline ligands that addition of a further heteroaromatic ring to a benzyl group of a SH3 domain ligand may be a very effective strategy for improving the strength of the binding interaction while not simply extending with further lipophilic structures. The promising results of utilising heteroaromatic rings instead of benzene rings when targeting the largely hydrophobic SH3 domain targets, as explored with these biaryl compounds and also with the compounds **22a** and **108b** in the previous chapter, demonstrates the efficacy of this strategy which could also be applied to PPI targets generally and therefore help overcome the significant challenge of designing drug-like small molecules targeting PPIs.

The more concordant K_d values obtained for assays of some derivatives compared to other similar compounds is likely due to improved solubility under the assay conditions. While the ligands were prepared for assays using 5% DMSO in the buffer solution to aid solubility, this was not sufficient to avoid precipitation of all the ligand compound especially at higher concentrations. It is therefore plausible that further studies using a higher concentration of DMSO might improve the solubility of the compounds under assay conditions and reduce the error margins. While this might give more precise determinations of the K_d values for those compounds, it does not aid the aim of the project to develop more effective and drug-like ligands for the Tec SH3 domain. The pyrimidinyl-extended compounds were soluble under assay conditions and gave the most promising results to address the aims of the project, and therefore designing alternate methods to improve solubility of the more lipophilic compounds under assay conditions was not investigated further.

Aside from the improvements to aqueous solubility and the apparent increase in the strength of the binding interaction for these large 6-position substituted 2-aminoquinolines, some further structural information was obtained from the assay results. Despite the limited number of structures, there are indications that the attachment position of the heterocyclic ring may have some effect upon the strength of the binding interaction, as the 2-position substituted compounds **115a** and **116a** had a slightly higher measured K_d value compared to the corresponding 3-position and 4-position analogues. This difference was consistent with the observations from the simpler benzylpiperidine ligands in the previous chapter, where the *ortho*-substituted ligand compounds also tended to have a weaker binding affinity for the Tec

SH3 domain. This could be due to steric clashes of the *ortho*-substituents on the benzene ring, and if steric hindrance were the key reason then this would be expected to have have a greater impact for the biaryl compounds, which appears to be consistent with the observations.

The bulky biaryl-extended piperidine ligands **114**-**116** assayed using the SPR method all appear to be readily accomodated upon binding to the Tec SH3 domain, even with *ortho*-substituted benzene rings. The consistency of these results would indicate that there is substantial free space in the binding region of the Tec SH3 domain, and therefore even larger 6-position substituents may be accommodated without unfavourable interactions of the ligand with the protein surface due to steric clashes. It is possible that further aromatic rings may be added to improve the strength of the binding interaction, although this is unlikely to be favourable for achieving more drug-like characteristics of the small-molecule ligand.

Initially, the investigation of these biaryl-extended piperidine compounds was proposed due to the interesting results of some biphenyl compounds which had been studied as part of a previous project. The biphenyl compounds **16a** and **16b** (see Figure 66) had unusual binding activity, hypothesised to be due to alternating binding of the compound to two binding regions which could not be simultaneously accessed. Despite the proposed sub-optimal binding to the Tec SH3 domain, the reported binding dissociation constants determined by the NMR chemical shift perturbation assays was very good, with the K_d values calculated to be 7 ± 2 μM for **16b** and 8 ± 3 μM for a mixture of both **16a** and **16b**.[57] Determination of the K_d values for **16a** and **16b** using the SPR assay method was attempted, however the compounds were not soluble under the assay conditions so a direct comparison could not be obtained.

If the K_d values for for the sub-optimal binding interaction of **16a** and **16b** with the Tec SH3 domain determined by the NMR assay method are reliable, it would be expected that simultaneously accessing both of the proposed binding interactions with an optimal ligand would result in a very significant decrease in the calculated K_d value for the more effective ligand due to the additional favourable binding interactions. Arguably, a K_d value even lower than 2.4 ± 0.2 μM would be expected, and this was the calculated K_d value for the strongest binding biaryl-extended ligand, **116c**. This comparison of results (Figure 76) may indicate that the biaryl-extended piperidine ligands still do not optimally access the binding interactions which were identified by the compounds **16a** and **16b**, and therefore further investigation of different biaryl-extended ligands may result in a much stronger binding ligand if the optimal configuration of the 6-position 2-aminoquinoline substituent can be determined.

Even though the results appear to suggest that the optimal 2-aminoquinoline ligand has still not been identified, significant improvements have been made. Firstly, several of the novel biaryl-extended piperidine ligands tested by the SPR assay method gave a lower K_d value than the extended phenoxy compounds **16a** and **16b**, potentially showing that this configuration is

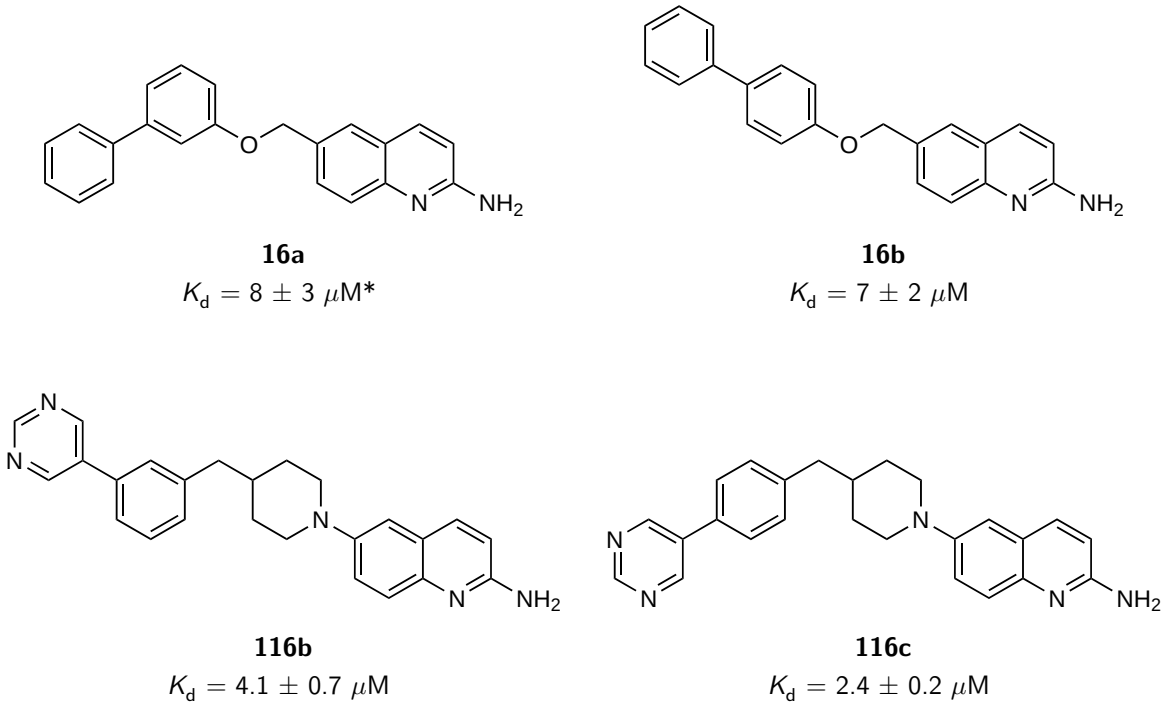


Figure 76: Comparison of K_d values for the previously studied phenoxy compounds (**16a** and **16b**) tested using NMR assays,[57] and the novel biaryl extended 2-aminoquinoline ligands (**116b** and **116c**) assayed using the SPR method as part of this project. *Assayed as mixture with **16b**.

a significant improvement although the K_d values obtained from the different assay methods may not be directly comparable. Secondly, the improvement in the strength of the binding interaction was achieved while also improving the aqueous solubility of the ligand, whereas the compounds **16a** and **16b** were insoluble under the SPR assay conditions. Finally, the results suggest that further improvements can be made. The range of different benzylpiperidine-type extended 2-aminoquinoline ligands which were found to effectively bind to the Tec SH3 domain have provided much needed information about favourable structures which improve the strength of the binding interaction. This new SAR information can be directly applied to the design of more potent and effective 6-position substituted 2-aminoquinolines targering the Tec SH3 domain, with very promising indications that a strongly binding ligand will be obtained and enable the structure of the protein-ligand complex to be determined.

4 Synthesis of extended 3-position 2-aminoquinolines

4.1 Introduction

Previous research into 3-position extended 2-aminoquinoline derivatives as Tec SH3 domain ligands identified that a simple substituted phenethyl group could result in improved binding affinity compared to the 2-aminoquinoline lead compound, and likely makes an additional favourable hydrophobic contact with the protein binding surface.[56] The strongest binding ligand, with a *tert*-butyl substituent on the phenethyl group, was the largest 3-position extended derivative that had been previously investigated (**137**, Figure 77). The use of large and hydrophobic groups, such as the *tert*-butylbenzyl group, is not preferable from a drug design perspective as water solubility is required, and therefore a range of alternate 3-position substituents investigating the use of similarly large substituents were proposed with more varied structures and particularly more hydrophilic structures.

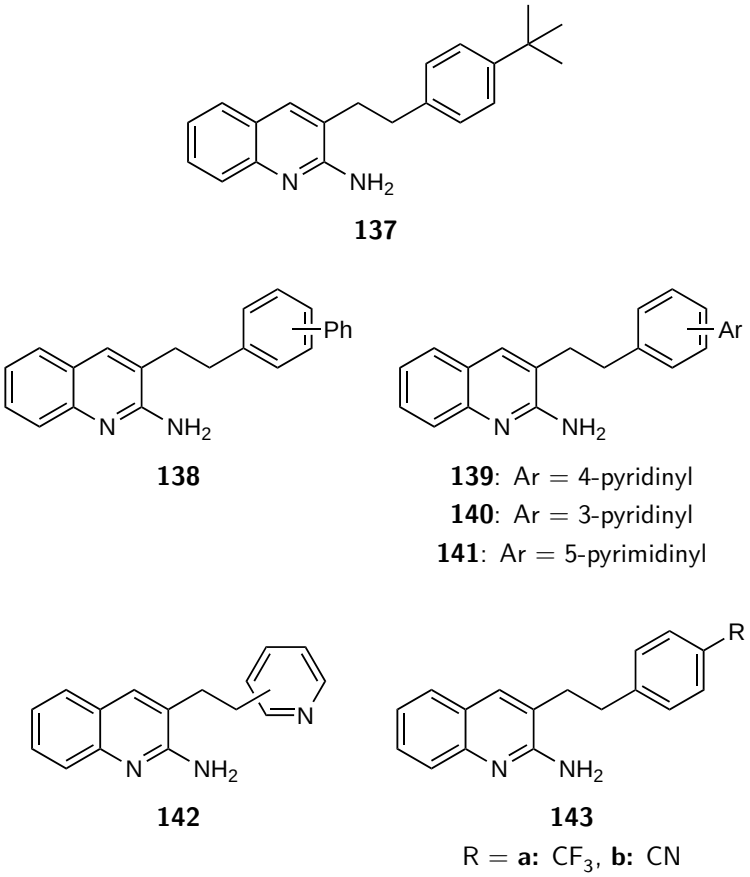


Figure 77: Strongest binding 3-position extended 2-aminoquinoline ligand identified by previous studies (**137**), and novel target compounds **138**-**143**.

Primarily, the introduction of biphenyl-substituents (**138**) was expected to access the same binding interactions with the SH3 domain binding surface as the ligand **137**, and these were

then compared to a range of biaryl-substituents (**139**-**141**) to assess whether the introduction of less lipophilic heteroaromatic rings will impact the ligand binding interactions. Secondly, the smaller ligands with a pyridinylethyl-substituent (**142**) had not been reported previously, but were proposed as ligands to investigate whether using a pyridine instead of a benzene ring may be an effective strategy of designing less lipophilic SH3 domain ligands without negatively impacting the binding affinity.

Finally, the additional proposed ligands **143a** and **143b** are supplementary to the simple extended phenethyl-substituted ligands reported previously, as those results indicated that adding a *para*-substituent to the benzene ring could improve the binding affinity of the ligand. Only simple alkyl- or fluoro-substituents had been previously investigated, therefore substituents which are electron withdrawing by induction (CF_3) or by resonance (CN) were required to provide more information about the binding interaction.

4.1.1 General synthetic pathways

Previously utilised synthetic methods for 3-position extended 2-aminoquinolines

To make simple 3-position phenethyl extended ligands previously, a Horner-Emmons method was utilised, followed by introduction of a 4-methoxybenzyl protected amino group (Figure 78).[56] Investigations into the products of various reaction pathways identified that the 2-position aryl chloride bond is not stable to hydrogenation conditions, and therefore the hydrogenation step had to occur after amination of the 2-chloroquinoline to a protected 2-aminoquinoline.

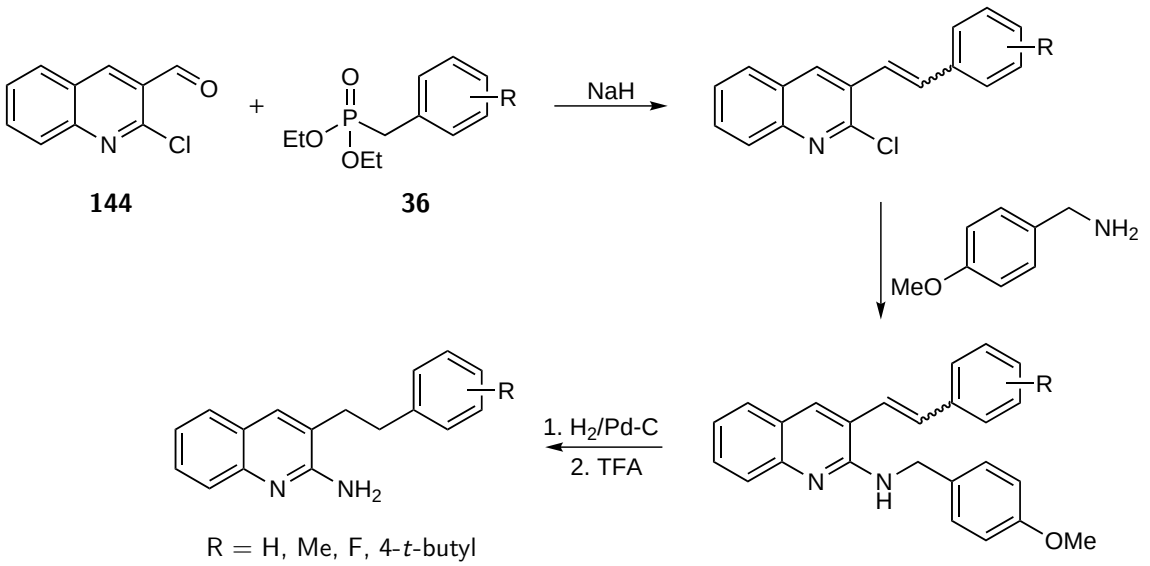


Figure 78: Previous synthesis of 3-position extended 2-aminoquinoline derivatives with simple phenethyl substituents via a Horner-Emmons reaction.[56]

It was anticipated that this synthetic pathway could be modified to incorporate methods effectively used in the earlier sections of this work in order to prepare the more structurally

complex target 2-aminoquinoline derivatives. Using the previously reported method, it was proposed that the quinoline intermediate **144** could be used to make all of the target 3-position extended 2-aminoquinoline derivatives. The synthetic process would therefore use a carbon-carbon bond forming reaction, such as a Horner-Emmons reaction, to attach each 3-position substituent to give the vinyl compounds. There were two key components of the synthetic pathway that required investigation in this project to make all of the novel compounds. Firstly, an alternate method for introduction of the 2-position amino functionality was proposed using the Buchwald-Hartwig amination procedure developed for 6-position substituted aminoquinolines previously, which would reduce the number of steps required to make the required target compounds. Secondly, investigation and development of the synthesis of additional phosphine reagents was required due to the wider range of novel 3-position substituents proposed.

Methods for 2-position amination of 3-position extended 2-chloroquinoline derivatives

In the previous synthetic procedure, the 2-position amino group was introduced as a *p*-methoxybenzyl-protected amine (Pathway 1, Figure 79), however this method necessitates an additional deprotection step in the overall synthetic pathway, and therefore it is desirable that the use of protecting groups would be avoided if possible.

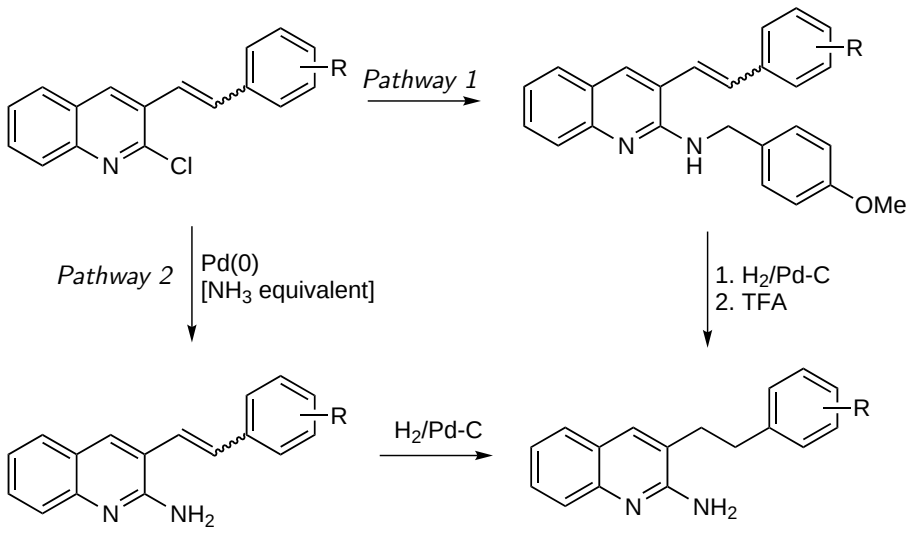
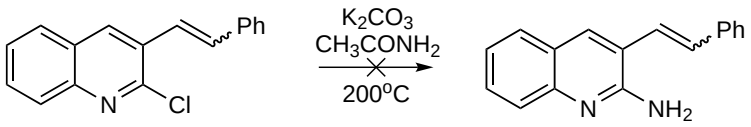


Figure 79: Proposed amination of the 3-position extended 2-chloroquinoline derivatives, via the previously reported method with *para*-methoxybenzyl amine[56] or via the proposed Buchwald-Hartwig amination procedure.

Alternate methods had also been attempted to introduce the 2-position amino group to 3-position extended quinolines with little success. The Kóródi method was attempted, however a complex mixture of products was reported, and it was suspected that decomposition occurred under the harsh reaction conditions (Scheme 89).[79,56]

The use of a Buchwald-Hartwig amination, similar to that used for 2-position amination of



Scheme 89: Previously attempted Kóródi amination method for conversion of 2-chloroquinoline derivatives to corresponding 2-aminoquinolines.[56]

6-substituted quinoline derivatives in previous sections of this project, had not been previously utilised. It was therefore anticipated that the Buchwald-Hartwig amination using LiHMDS as the ammonia equivalent and base could also be used to synthesise the 3-position substituted 2-aminoquinolines from 2-chloroquinolines. This would remove the necessity for the additional deprotection step, shortening the overall synthetic pathway (Pathway 2, Figure 79).

Methods for incorporation of various 3-position substituents to quinoline reagent

For the first group of ligands **138**-**141**, it was proposed that a Suzuki reaction could be used to synthesise the biphenyl or biaryl group from an arylboronic acid derivative and an aryl bromide, in a very similar method to the synthesis of biaryl-extended piperidine derivatives in a previous chapter (see Scheme 85). There are several possible synthetic pathways incorporating this key step, varying in the order of reactions (Figure 80).

For efficiency, it was ideal that Suzuki reactions with the full range of boronic acid derivatives would occur at a late stage in the synthetic pathway (Pathway 2 or 3, Figure 80) as this late stage derivatization reduces the number of intermediates required. In this case, however, the quinoline intermediate (**145**) also contains a 2-position aryl chloride bond and therefore it was anticipated that competing reactivity of aryl halides in **145** may result in lower yields of desired products and complications in purification of compounds. The alternate pathway uses the Suzuki reaction to synthesise the biaryl structure prior to reaction with the quinoline reagent **144** (Pathway 1), and would only ever result in a maximum of one aryl halide bond in each intermediate compound, therefore those competing side-reactions for the Suzuki or amination reactions would not be expected to occur.

For the second type of proposed ligands with a 3-position pyridinylethyl substituent, **142**, it was known from a previous section of this work that the corresponding phosphonate reagents required for the Horner-Emmons reaction could not be effectively synthesised and isolated. Instead, using a Wittig reaction for this group of target compounds was a more feasible strategy as the Wittig reagents were obtainable (Figure 81). The reaction conditions vary from the Horner-Emmons reaction and therefore require added investigation, and removal of the triphenylphosphine oxide by-product is required in the work-up procedure, but in all other respects the proposed synthetic pathway is the same as for the biaryl derivatives.

The final group of target ligands are also the simplest, and the most similar to the derivatives

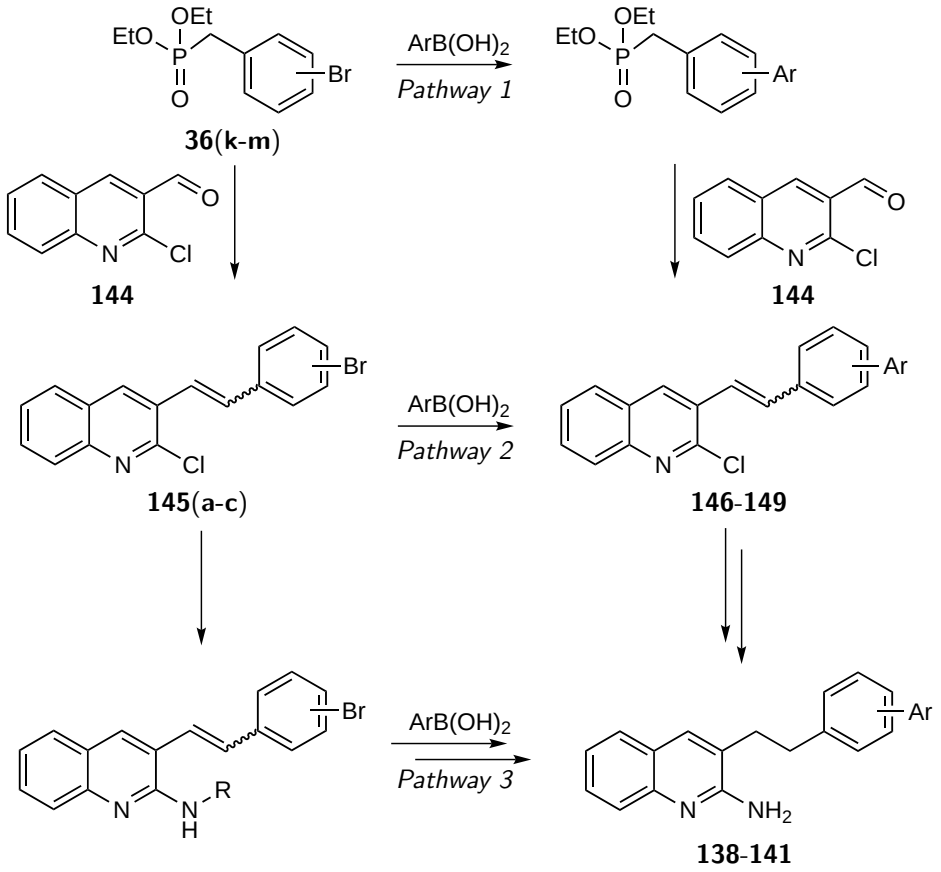


Figure 80: Proposed synthetic pathways for 3-position extended 2-aminoquinoline derivatives with biaryl groups based upon previously reported Horner-Emmons method and the Suzuki methods established in this project.

made in the previous work which identified the strongest binding ligand. These only vary from the previously made SH3 domain ligand **137** by the functional group on the 3-position phenethyl substituent, and therefore it was anticipated that the same reaction sequence as reported for that compound could be utilised to make the simpler targets with CF_3 and CN substituents (Figure 81).

4.2 Synthesis of biaryl extended 2-aminoquinoline derivatives

4.2.1 Investigation of synthetic pathways for 3-position extended quinoline derivatives

To investigate the viability of the proposed synthetic pathway, the synthesis of two derivatives **138c** and **139c** was first attempted via the first pathway, from the intermediate compounds **144** and **36m**. It was expected that a pathway which is effective in the synthesis of these two compounds could then be applied to the synthesis of the remaining similar derivatives. The synthesis of neither of these compounds had been reported previously, but one of the

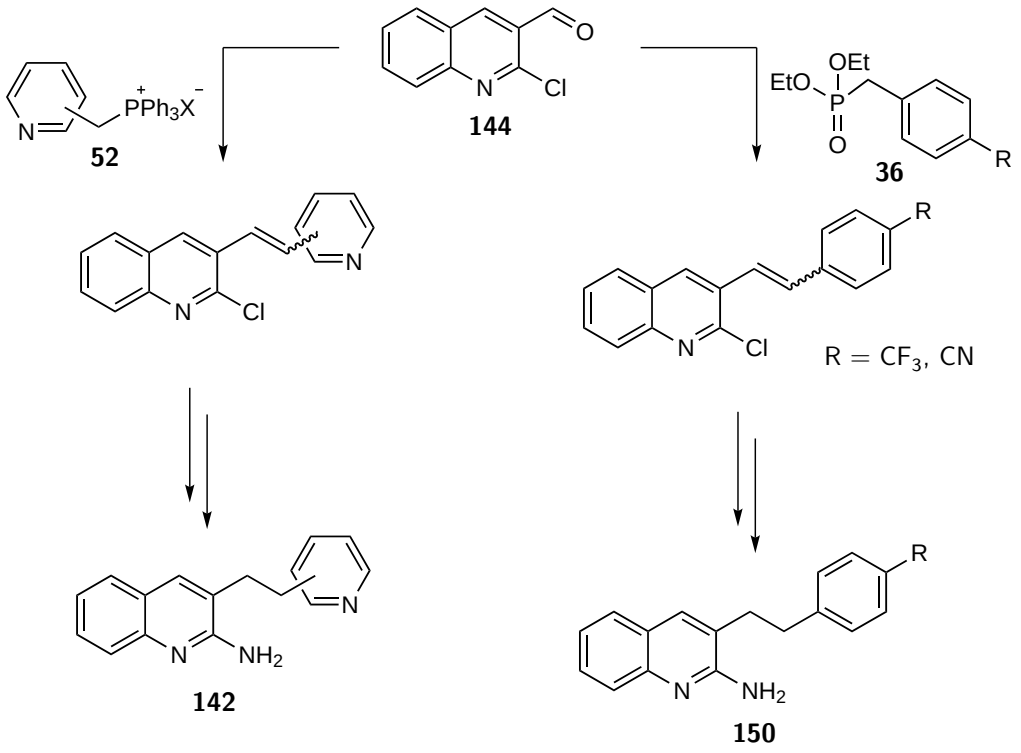
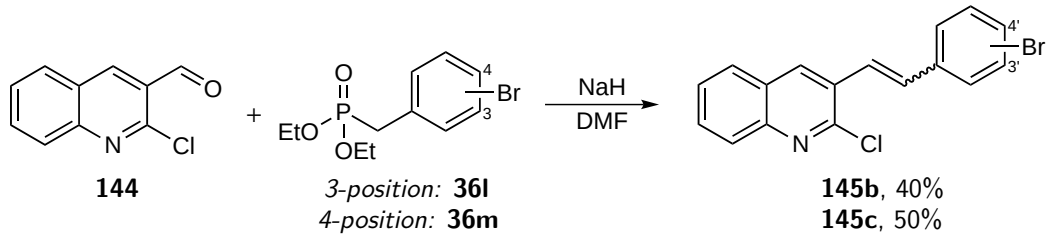


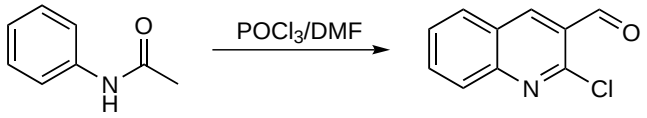
Figure 81: Proposed synthetic pathways for simple 3-position extended 2-aminoquinoline derivatives **142** and **150**.

intermediate compounds **145c** had been made in moderate yield (50%) previously, and therefore the reported reaction conditions were initially used for investigations into viability and optimisation of this step (Scheme 90).[56]



Scheme 90: Previously reported synthesis of bromo-substituted 3-phenylvinyl-2-chloroquinolines (**145**) via a Horner-Emmons reaction.[56]

The synthesis of the key aldehyde intermediate, 2-chloro-3-formylquinoline (**144**), had been reported in the literature previously.[77] The one-step literature method from acetanilide and phosphoryl chloride with DMF was used to yield the **144** via a Vilsmeier-Haack formylation reaction with moderate yield (42%, Scheme 91). The presence of the key reactive functional groups was determined by spectroscopic analysis. Distinctive isoptope masses were found in HRMS analysis to confirm the presence of the 2-position chloro-substituent, and the ^{1}H NMR spectrum showed a signal corresponding to the hydrogen of the aldehyde functional group ($\delta_{\mathrm{H}} = 10.57$ ppm), which is the necessary functional group for the subsequent carbon-carbon bond forming reactions.



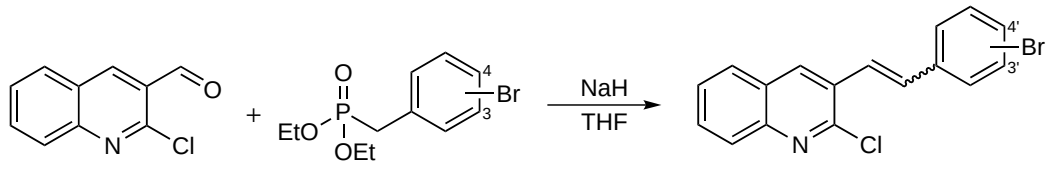
144
42%

Scheme 91: Synthesis of 2-chloroquinoline-3-carboxaldehyde intermediate (**144**) used in the synthesis of all 3-position extended 2-aminoquinoline derivatives, by Vilsmeier-Haack formylation reaction.[77]

Investigation of Horner-Emmons reaction pathway for synthesis of 3-position extended 2-aminoquinoline derivatives

Following the proposed pathway (as in Pathway 1, Scheme 80), the next step is the attachment of the 3-position substituent by a Horner-Emmons reaction with a bromo-substituted benzylphosphonate reagent. In this case, reactions with the phosphonate reagents **36l** and **36m** were first investigated. These Horner-Emmons reactions had been reported previously,[56] with moderate yields, using typical Horner-Emmons reaction conditions of sodium hydride as base and DMF as the solvent. In previous sections of this work, however, investigations into syntheses of benzylpiperidines via a Horner-Emmons reaction identified that high yields of the desired products was achieved using THF as the solvent (for example, **45c** obtained in 87% yield, see page 37). From those results, it was anticipated that similar reaction conditions may result in higher yields of the Horner-Emmons reaction products in this case also.

These Horner-Emmons reaction conditions were used in the attempted synthesis of **145b** and **145c** from quinoline **144** and the corresponding phosphonate derivatives, however only a low yield (25%) of the desired products could be obtained (Scheme 92).



144 | *3-position:* **36l**, *4-position:* **36m** | **145b**, 25%, **145c**, 25%

Scheme 92: Attempted synthesis of 3-position extended 2-chloroquinolines via Horner-Emmons reaction with sodium hydride.[56]

In each case both isomers of the desired product were isolated, with more *E*-isomer product obtained from the reaction. The two isomers could be readily distinguished by the vicinal coupling constant for the alkene hydrogen signals in the ^{1}H NMR spectrum. The *E*-isomer has a larger vicinal coupling constant for the two alkene doublet signals ($^3J_{H,H}$ = 16.2 Hz) and distinct chemical shifts for each signal. In contrast, the alkene signals for the minor *Z*-isomer appeared further upfield and had a small chemical shift difference between the alkenyl signals, therefore appearing as a distinctive strongly coupled AB system in the ^{1}H NMR spectra. Non-first order analysis could be used to determine the chemical shifts

of the alkene signals for characterisation, and the vicinal coupling constant was measured to be smaller than the coupling constant for the corresponding *E*-isomer ($^3J_{H,H}$ = 12.5 Hz), thereby enabling definitive assignment of signals for each product isomer and determination of the major isomer of the product obtained from the reaction. Compared to the quinoline reagent **144**, the products had an upfield shift of the H_4 signal due to the loss of the aldehyde functional group, and 2D NMR experiments were used to confirm successful formation of the new carbon-carbon double bond at the C_3 position (Figure 82A). The HRMS analysis of the product was used to determine that both the bromine and chlorine were present in the isolated products, with masses and abundances of peaks consistent with the major isotopic masses of the halogenated products.

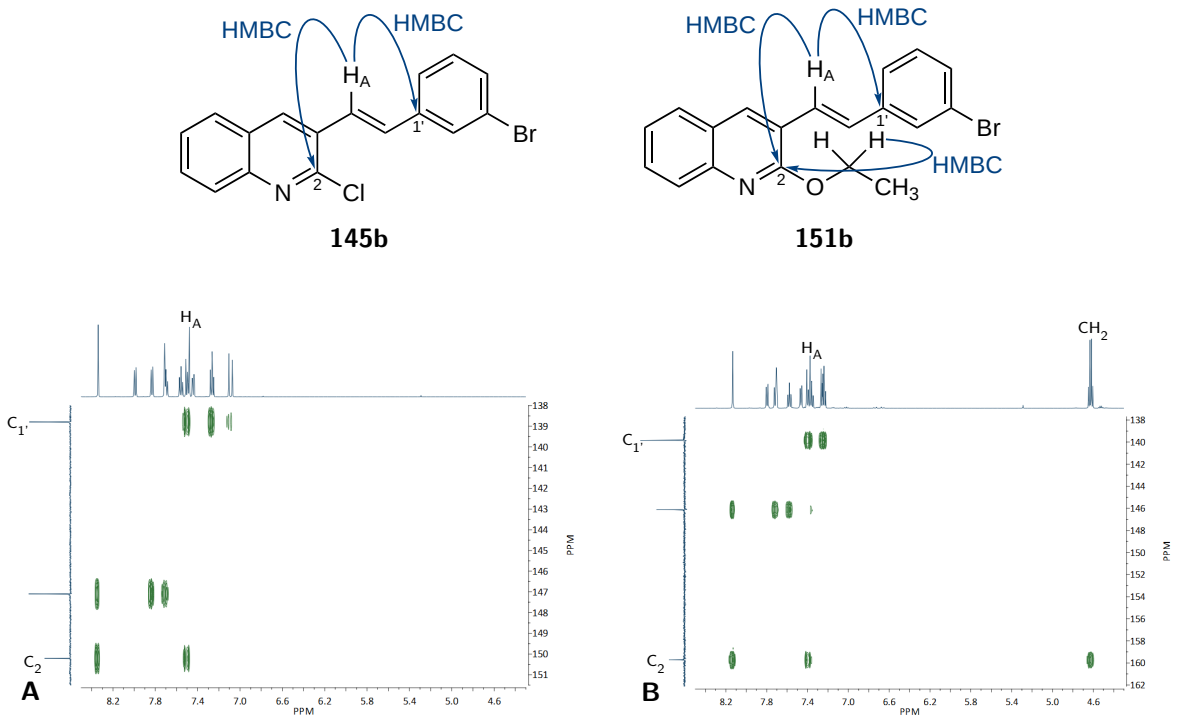
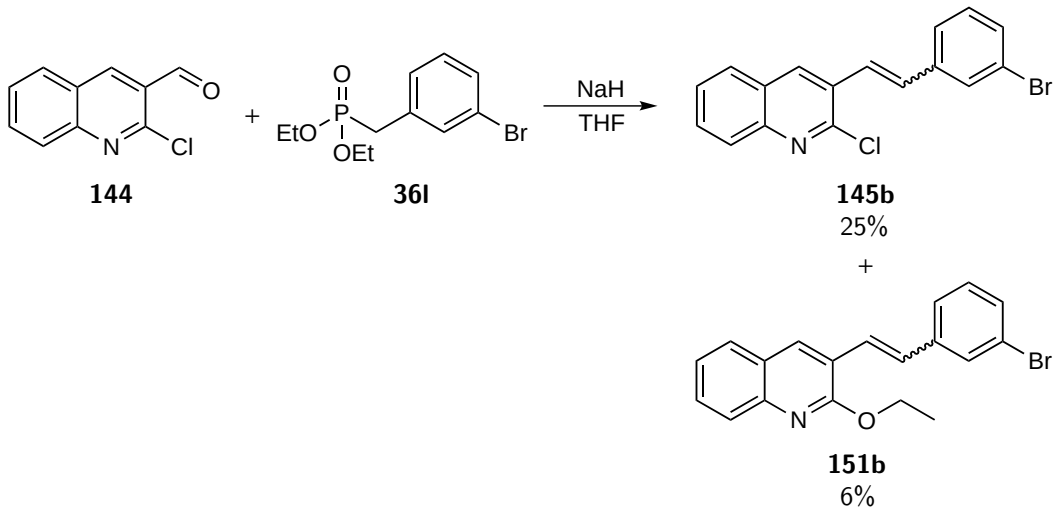


Figure 82: HMBC correlations observed for 3-position substituted quinoline products of a Horner-Emmons reaction.

A longer reaction time was required for the reaction of **144** and **36l** to go to completion, determined as complete consumption of **144** by TLC analysis, and under these conditions a sample of an undesired quinoline side-product was also isolated (Scheme 93). Signals consistent with the quinoline ring and a bromo-substituted 3-phenylvinyl substituent were observed in the crude NMR spectrum from the reaction, similar to those observed for the expected product **145b**, but additional signals upfield were also observed. The similarity in aromatic signals observed for the two products demonstrated that the side-product was also likely formed by the successful Horner-Emmons reaction of **144** and **36l**, but a further reaction had also occurred.

The integration and multiplicity of the signals in the ^{1}H NMR spectrum of this side-product



Scheme 93: Synthesis of 3-position extended 2-chloroquinoline **145b** via Horner-Emmons reaction with sodium hydride, for extended reaction time (16 hr).

were distinctive for an ethyl group, and the comparatively downfield shift of the CH_2 quartet signal compared to the CH_3 triplet signal showed it was significantly deshielded, consistent with an ethoxy group. 2D NMR experiments were used to demonstrate that the ethoxy group showed HMBC correlations between the CH_2 quartet and the C_2 signal, indicating that this side-product could be due to a nucleophilic aromatic substitution reaction at the 2-position of the quinoline ring to give the 2-ethoxy substituted side-product **151b** (Figure 82B). A nucleophilic substitution reaction at the 2-position of the quinoline ring is not unexpected as the reactive aryl chloride bond is further activated by the neighbouring quinoline nitrogen, and in previous sections of this project undesired side-reactions had also occurred at this position (for example, see Scheme 59, page 92).

Further investigation showed that prolonged Horner-Emmons reaction times (up to 16 hours) using NaH as the base resulted in a much larger quantity of this side-product being isolated from the reaction mixture, whereas **151b** was not observed for short reaction times (1 hr). It was expected that the formation of this product was potentially due to hydrolysis of the excess phosphonate reagent by the sodium hydroxide which is present as an impurity in the base, followed by nucleophilic aromatic substitution at the 2-position aryl chloride bond of the desired product **145b**. The desired product is produced much faster in the reaction mixture, and therefore shorter reaction times meant this undesired further reaction could not occur.

The low yields of the desired 2-chloroquinoline **145b** and **145c** products under these Horner-Emmons reaction conditions was unexpected, as complete consumption of the limiting reagent **144** was observed both by TLC monitoring of the reaction progress and by analysis of the crude ^{1}H NMR spectrum after work-up. The distinctive downfield aldehyde signal and other characteristic signals of the starting material **144** were absent from the spectra, but signals consistent with a large amount of another simple quinoline compound were evident in the

^{1}H NMR spectra of the reaction mixtures. It was observed that signals with a splitting pattern corresponding to the second ring of the quinoline were present at slightly different chemical shifts, and a singlet peak at a similar shift to the H_4 signals of the desired products was also present. It was anticipated from this that the low yield was due to an undesired side-reaction involving the limiting reagent **144** which would give this other quinoline type product. The identity of the product could not be determined from the crude reaction mixtures due to the overlap in signals from this side-product and the desired products, and also due to a large amount of unreacted phosphonate reagent present. The side-product could not be separated from the phosphonate reagent by attempted chromatographic separation.

The large amount of unreacted phosphonate reagents **36l** and **36m** in the reaction mixtures was unexpected, as these phosphonates had been used successfully in Horner-Emmons reactions with ketones under the same conditions and therefore it was known that NaH was a sufficient base to deprotonate the phosphonate. Due to the reactivity of the quinoline **144**, however, the use of different bases was investigated to determine whether an alternate base would promote the desired reaction to make **145c**. The results show that the base has a significant impact upon the product distribution, although in each case the side product was observed (Table 30). LiHMDS (added as a solution in THF) gave complete consumption of the quinoline reagent but only a small amount of the desired product **145c** was observed, whereas sodium *tert*-butoxide gave a similar result to that observed with sodium hydride.

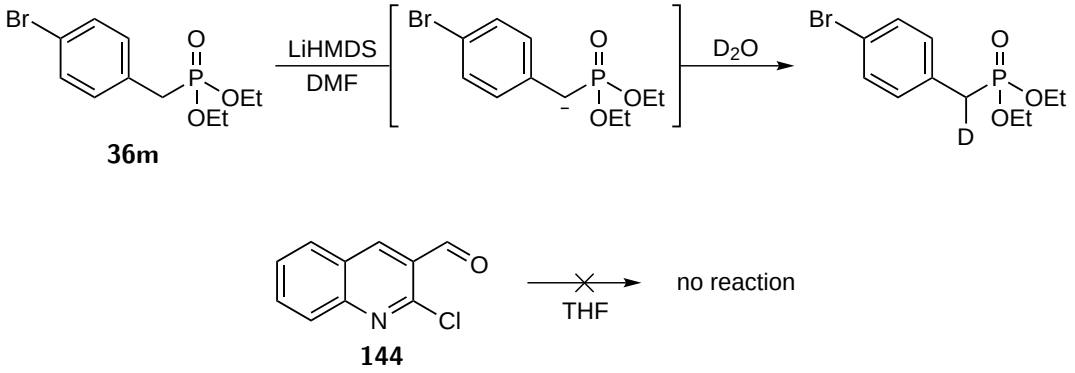
Table 30: Comparison of product distribution from Horner-Emmons reaction based upon solvent and base.

Solvent	Base	Ratio 145c:152[b]	Isolated yield of 145c (%)	Ratio (*E*-/*Z*)-145c
THF	LiHMDS[a]	1:4	-[c]	7:3
	NaH	7:3	25	4:1
	NaO^{t}Bu	4:7	36	4:1
DMF	LiHMDS[a]	7:3	-[c]	2:1
	NaH	1:0	77	7:3
	NaO^{t}Bu	1:0	78	7:4

[a] LiHMDS was added as a 1M solution in THF; [b] Determined by comparing integration of distinct peaks in the ^{1}H NMR spectrum of the crude product mixture after work-up, as complete recovery and purification of **152** by column chromatography was not achievable; [c] Purification of sample not attempted due to low conversion to desired product.

The results using LiHMDS as the base required further investigation to determine which reaction factors contributed to the poor yield obtained in synthesis of **145c**. Firstly, the reaction of base with phosphonate **36m** was checked, and a visible colour change of the solution to red was observed upon addition of the base to **36m**, a typical observation upon formation of the phosphonate anion. Quenching the mixture with D_2O and analysing the

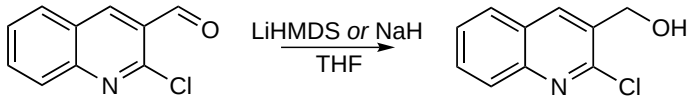
crude mixture with ^{1}H NMR spectroscopy showed the presence of a broader HP doublet slightly upfield of the HP doublet observed for **36m**, showing that the deuterated phosphonate was present and therefore that the base LiHMDS had been sufficient to deprotonate the phosphonate reagent in the reaction mixture (Scheme 94). Another test of whether **144** was reacting in the solvent without base added was undertaken, and it was found that stirring the reagent in THF for 5 hr (longer than the reaction time to make the side-product previously) resulted in complete recovery of the reagent **144**.



Scheme 94: Tests used to confirm reactivity of quinoline reagent **144** and phosphonate **36m** under Horner-Emmons reaction conditions.

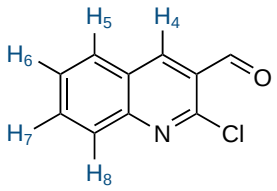
The final test of reaction conditions investigated whether the quinoline reagent would react under the Horner-Emmons reaction conditions in the absence of the phosphonate reagent, and this was investigated using NaH or LiHMDS as the base in the reaction mixture. In each case, the reagent **144** was almost completely consumed and the ^{1}H NMR spectrum of the crude product mixtures contained only one major product with a small amount of unreacted reagent **144** (Scheme 95, Figure 83B). As there were no further major products or recovered reagents complicating the NMR spectra it was possible to characterise the product. With comparison to the quinoline reagent (Figure 83A), the ^{1}H NMR spectrum of the product had substantially similar signals consistent with a 3-substituted quinoline compound, specifically the four coupled signals for the second quinoline ring and the H_4 singlet signal. Of those signals, the H_4 signal had the largest shift difference compared to the reagent, and the upfield shift of this signal demonstrated that the electron-withdrawing aldehyde substituent was no longer present in the product. In addition, the product had a large 2H signal appearing much further upfield at 4.93 ppm, which would be consistent with reduction of the aldehyde to an alcohol. The NMR data was entirely consistent with previous literature reports for (2-chloroquinolin-3-yl)methanol **152**,[56] and HRMS analysis of the quinolinol demonstrated that the mass was consistent with the structure of **152**, including the expected 3:1 isotopic mass peaks for the chloro-substituted compound.

Once the identity of the side-product had been confirmed, it was possible to determine the approximate ratio of the quinolinol side-product to the desired product **145c** in the crude

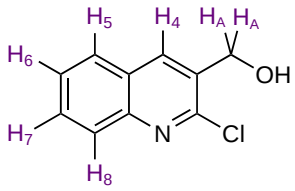


144 **152**

Scheme 95: Tests used to determine identity and conditions required for synthesis of quinolinol side-product **152**.



144



152

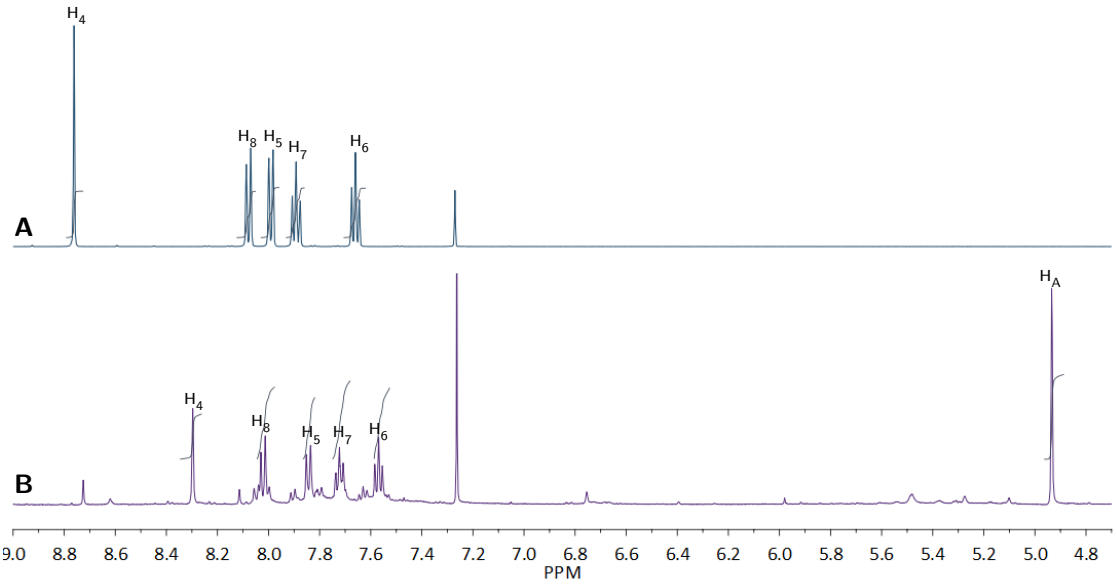
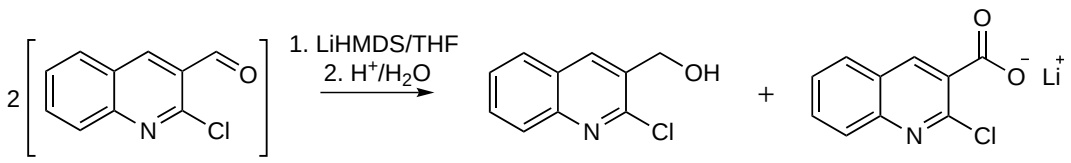


Figure 83: Comparison of ^{1}H NMR spectra for A: quinoline reagent **144**, and B: the reaction mixture after treating **144** with LiHMDS in THF, giving the product **152**.

product mixture for each attempted Horner-Emmons reaction by integration of the signals for the two products (Table 30). The mechanism for formation of the quinolinol side product was not evident from these results, however the synthesis of an alcohol from an aldehyde under basic conditions could be achieved by a Cannizzaro-type disproportionation reaction. While LiHMDS is not used as a base in Cannizzaro reactions, one Cannizzaro-type disproportionation reaction in the presence of LiHMDS has been previously reported, although low yields were obtained unless a lanthanide chloride was also added.[93] A Cannizzaro reaction would be expected to give an additional carboxylate-substituted product **153** (or the analogous amide, as previously reported for the Cannizzaro reaction using LiHMDS under different reaction conditions).[93] Due to the aqueous work-up, however, another quinoline product was never observed and therefore could not be used to confirm the hypothesis (Scheme 96).

These results indicate that the solvent may be promoting or enabling the side-reaction to



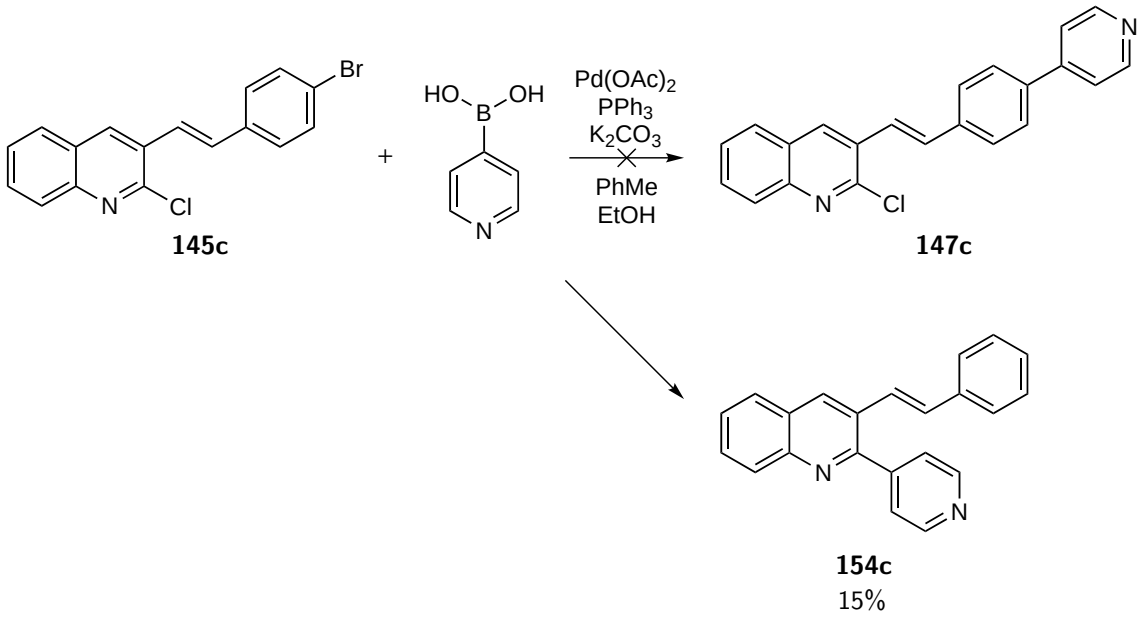
144 **152** **153**

Scheme 96: Proposed Cannizzaro-type disproportionation reaction of aldehyde-substituted 2-chloroquinoline **144** under Horner-Emmons reaction conditions to give isolated quinolinol product **152**, and un-isolated proposed product **153**.

occur, and so a comparison of reaction conditions with a different solvent, DMF, were obtained (Table 30). The direct comparison between solvents gave the unexpected result that using DMF gives significantly more conversion to the desired product. With sodium *tert*-butoxide or sodium hydride as the base, the reactions in DMF only gave the desired alkene products with good yield and none of the quinolinol product **152** was obtained. The quinolinol product was still observed when LiHMDS was used as the base, however as the LiHMDS was added as a commercially available solution in THF it is possible that the presence of THF is promoting the formation of quinolinol. A clear improvement using primarily DMF instead of THF as the reaction solvent even in this case demonstrates the large contribution of the solvent to the distribution of reaction products.

From the successful synthesis of **145c** via Horner-Emmons reaction, the Suzuki coupling of **145c** and 4-pyridinylboronic acid to make the biaryl compound was attempted to synthesise **147c** (Scheme 97). Initially, the reaction conditions used previously to synthesise biaryl-extended piperidine compounds via a Suzuki reaction were attempted (see Figure 85, page 137), however this gave a complex mixture of products. From the mixture, there was only one product (**154c**) produced in a sufficient quantity to be isolated by column chromatography and characterised.

The major product was confirmed to be an alkene due to the presence of the distinctive doublet signals with large coupling constants in the ^{1}H NMR spectrum, and both isomers of this major product were observed to be present in the mixture. Only the major isomer could be isolated by column chromatography and this was confirmed to be the *E*-isomer of the product, distinguished by the larger alkene coupling constant compared to the minor isomer ($^{3}J_{H,H} = 16.1$ Hz, compared to $^{3}J_{H,H} = 12.2$ Hz for the *Z*-isomer). The alkene signals and the distinctive coupling pattern corresponding to the 2-,3-substituted quinoline ring clearly demonstrated that the isolated compound was a product of a reaction of the quinoline reagent **145c**. Additional 2H signals with chemical shifts consistent with a 4-substituted pyridine ring were also present which strongly indicated a coupling reaction with the 4-pyridine boronic acid reagent had occurred, however the other expected 2H signals consistent with the *p*-substituted benzene ring of the expected product **147c** were not present. Instead of the expected benzene ring signals, the other aromatic signals had an integration and coupling pattern consistent with



Scheme 97: Attempted Suzuki reaction, with proposed structure of major product (**154c**) isolated from the reaction mixture.

a mono-substituted benzene ring. HRMS analysis of the isolated product identified a mass peak of 309.1390, without the 3:1 relative abundance peaks expected for the major isotopes of a chloro-substituted product or 1:1 relative abundance peaks expected for a brominated product despite both halogens being present in the reagent **145c**.

2D NMR experiments were used to confirm the structure of the side-product **154c**. HMBC correlations showed that the coupling reaction of the 4-pyridine boronic acid had occurred at the 2-position aryl chloride, instead of the desired coupling with the 3-position aryl bromide substituent (Figure 84). HMBC and COSY correlations also demonstrated that the aryl bromide bond had been lost, and therefore the product had an unsubstituted styryl substituent at the 3-position of the quinoline ring. The synthesis of this product indicated that the Suzuki coupling preferentially occurs at the 2-position of the chloroquinoline, and the aryl bromide bond of the 3-position substituent was not retained under the reaction conditions.

The amount of major product recovered for this reaction was low, however no other products could be isolated from the complex mixture. Identification of further products by ^{1}H NMR analysis of the crude mixture was not possible due to the large number of structurally similar potential products, and it would be expected that both *E*- and *Z*-isomers of each quinoline product would be present because a mixture of both isomers of the reagent **145c** was used. Instead, the presence of further products was investigated using HRMS analysis of the crude reaction mixture, as the characteristic isotopic abundances of potential products were expected to be evident and give an indication of the selectivity of the reaction (Table 31). Mass peaks consistent with the isolated major product **154c** were present, and the two isotopic mass peaks for the desired chloro-substituted product **147c** were observed, which indicates that

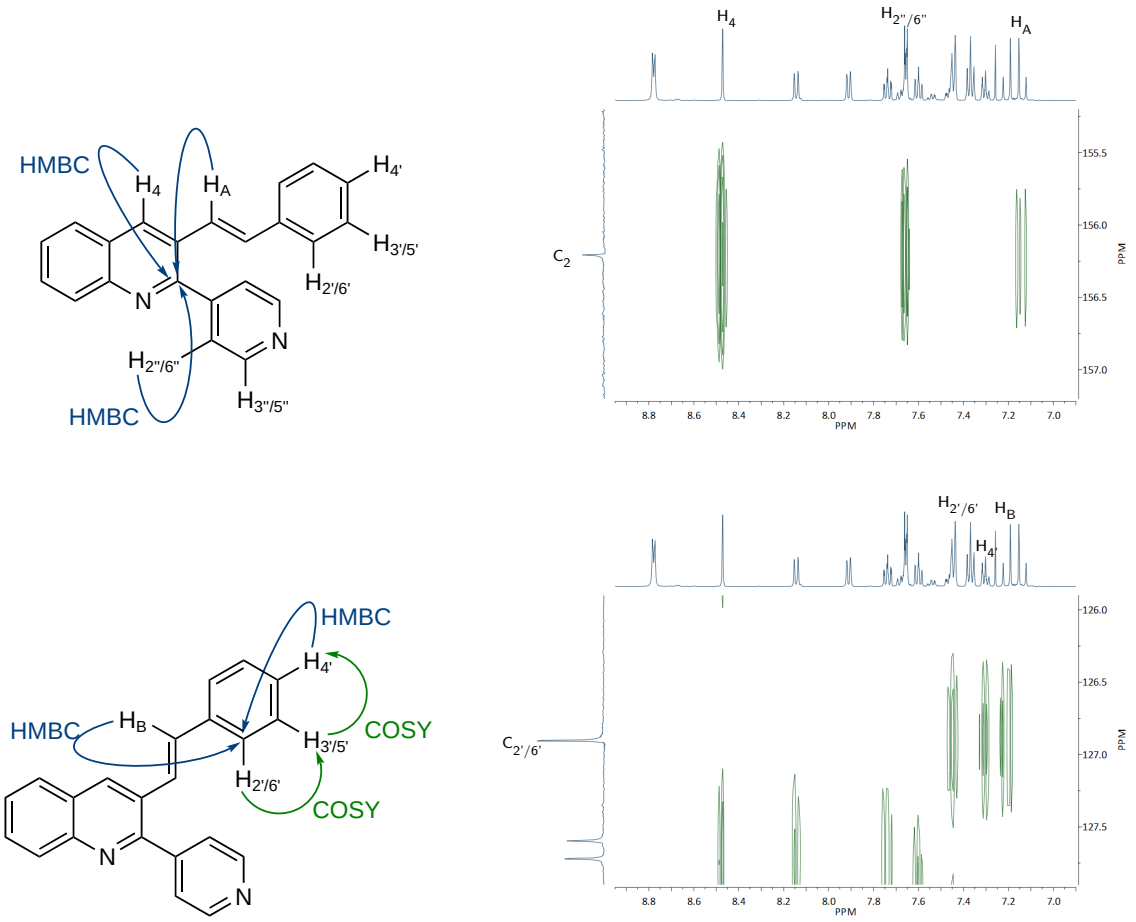
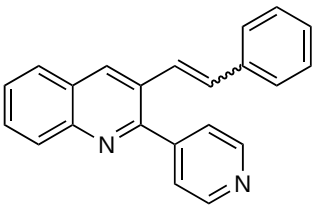
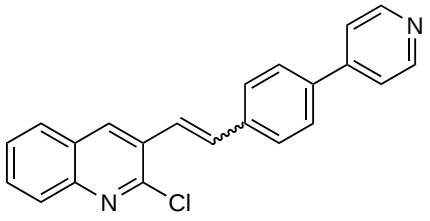
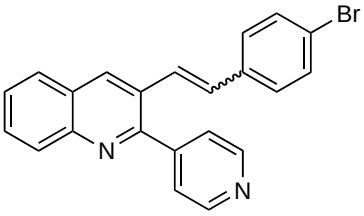


Figure 84: Key HMBC correlations used to determine structure of **147c**, the major product from attempted quinoline Suzuki reaction. Key observed [^{1}H,^{1}H]-COSY correlations also indicated.

some of the desired Suzuki coupling reaction may have occurred. The masses consistent with the ^{79}Br and ^{81}Br isotopes of the undesired 2-substituted side-product **155c** were also observed. The results demonstrate that the Suzuki reaction under these conditions favours reaction with the 2-position aryl chloride of the quinoline ring rather than the aryl bromide as desired, and also that the compounds are susceptible to loss of the aryl bromide bond using this method.

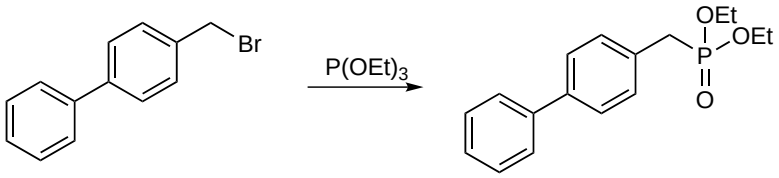
Table 31: Structures of potential products from Suzuki reaction and mass peaks identified by HRMS analysis of crude reaction mixture.

$[M+H]^+$ found	Corresponding molecular formula	$[M+H]^+$ calculated	Postulated structure
309.1390	$C_{22}H_{16}N_2$	309.1392	 **154c**
343.0998 345.0985	$C_{22}H_{15}{}^{35}ClN_2$ $C_{22}H_{15}{}^{37}ClN_2$	343.1002 345.0973	 **147c**
387.0517 389.0474	$C_{22}H_{15}{}^{79}BrN_2$ $C_{22}H_{15}{}^{81}BrN_2$	387.0497 389.0476	 **155c**

Regioselective Suzuki reactions had been previously reported in the literature, including selectivity for an aryl bromide over an activated aryl chloride.[94,95,96] Several reaction conditions were attempted for the synthesis of **147c** using alternate catalysts, solvents, and procedures that had been previously used in selective Suzuki reactions, however the crude reaction mixtures in each case were still complex and contained many products which could not be isolated. Due to the low amounts of the desired product produced in these reactions, and the inability to properly separate the many similar components of the crude mixture, it was determined that the alternate pathway (Pathway 1, Figure 80) was likely to be more successful. Although the alternate pathway required more intermediate compounds to be synthesised, it was anticipated this method would avoid yield loss due to competing side-reactions.

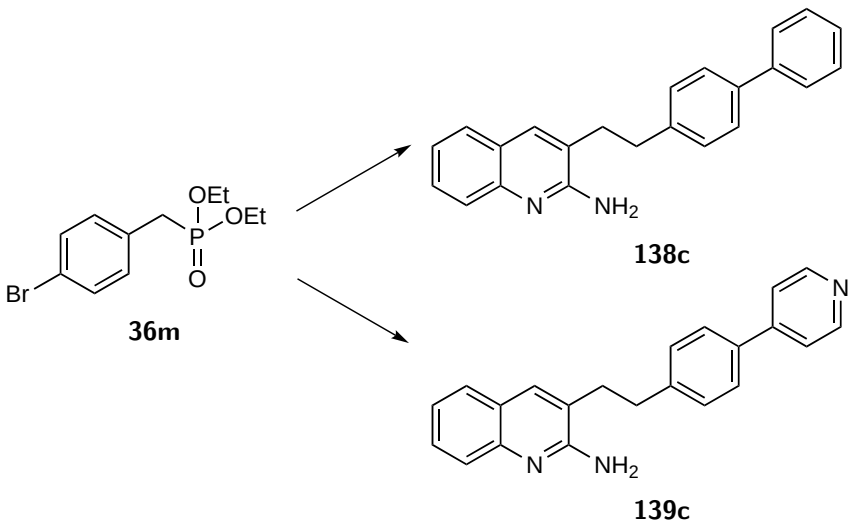
Alternate reaction pathway for synthesis of 3-position extended 2-aminoquinoline derivatives

The alternate pathway required synthesis of the biaryl-extended phosphonate derivatives **156**-**159** prior to the Horner-Emmons reaction with **144** to give the 2-chloroquinoline derivatives **146**-**149**. Of the target biaryl-phosphonate derivatives, only the biphenyl derivatives **156(a-c)** had been synthesised previously, and these were typically made from the commercially available bromomethylbiphenyls (Scheme 98)[97] or corresponding alcohols.[98] The heterocyclic biarylphosphonate derivatives had no reported syntheses, and the range of corresponding bromomethylbiaryls were not commerically available to use via the literature method. It was expected that instead of the literature synthetic pathway, the bromo-substituted benzylphosphonate derivatives **36(k-m)** could be reacted with the aryl boronic acids via a Suzuki reaction, and the products **156**-**159** would then be reacted with quinoline reagent **144** using the Horner-Emmons reaction as the key bond-forming step of the synthesis. As this synthetic procedure had not previously been attempted, initially the synthesis of only two 2-aminoquinoline derivatives was investigated to determine whether the procedure would be feasible, both of which would be synthesised from the same phosphonate reagent **36m** (Figure 85).



156c
99%

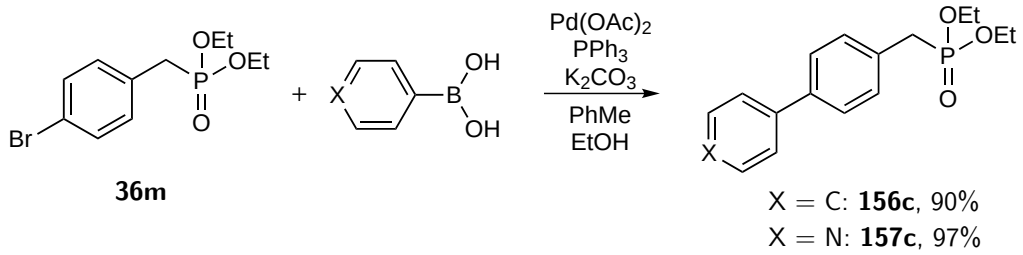
Scheme 98: Reported synthesis of biaryl-extended phosphonate derivative **156c**.[97]



36m **138c** **139c**

Figure 85: Initial target derivatives **138c** and **139c** used for investigation of alternate Horner-Emmons synthesis pathway.

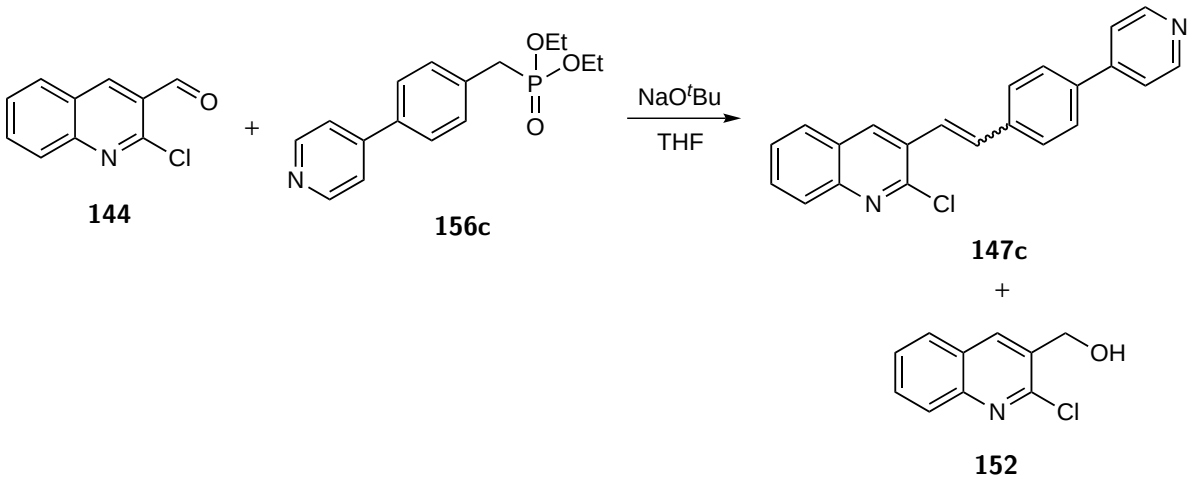
Using the same Suzuki reaction conditions developed previously (see Scheme 85, page 137), the syntheses of the two required phosphonate derivatives **156c** and **157c** from the phosphonate **36m** and the corresponding arylboronic acids were attempted (Scheme 99). It was found that the reaction conditions were also highly effective in the synthesis of these biaryl phosphonates and gave high yields of the desired products after purification by column chromatography (**157c**: 97%, **156c**: 90%), and therefore further optimisation of the reaction conditions was not required. Success of the reaction was clearly shown in the NMR spectra of the products, as in each case there was a slight downfield shift of the PCH_2 doublet signal in the ^{1}H NMR spectrum compared to **36m**, and the appearance and integration of the aromatic peaks was consistent with the expected biaryl structures. Evidence of the successful coupling of the second aromatic ring was best demonstrated by the splitting of the ^{13}C NMR signal corresponding to the quaternary carbon of the second ring. In both cases this signal appeared as a doublet due to coupling with the phosphorous atom ($^6J_{C,P} = 1.5$ Hz for both structures).



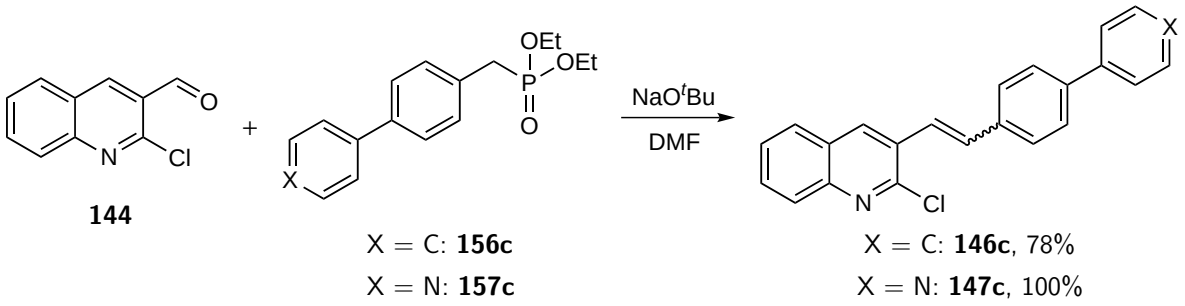
Scheme 99: Synthesis of biaryl-extended phosphonate derivatives **156c** and **157c** via Suzuki reaction.

From the phosphonates, the Horner-Emmons reaction with **144** could be attempted as the key carbon-carbon bond forming reaction to make the target 3-position extended 2-aminoquinoline derivatives. Similarly to the synthesis of **145**, a brief test of reaction conditions for the synthesis of **147c** from **144** and **157c** demonstrated that the reaction in THF gave more quinolinol product (**152**) than the desired alkene products, with a large recovery of unreacted phosphonate reagent (Scheme 100). In contrast, the preferred reaction conditions using DMF as the solvent resulted in high isolated yields of 78% and 100% for **146c** and **147c** respectively, with none of the quinolinol product observed in the reaction mixture for either derivative (Scheme 101).

Two isomers of each alkene product were obtained from the Horner-Emmons reactions of **144** and each phosphonate derivative. In each case the reaction favoured formation of the *E*-isomer as expected for the Horner-Emmons reaction, although some *Z*-isomer was also produced, as evidenced by the distinctive doublet peaks in the ^{1}H NMR spectra of the products ($^3J_{trans} = 16.3$ Hz for **146c** and 16.2 Hz for **147c**, $^3J_{cis} = 12.1$ Hz for both products). For the quinoline signals, conversion of the 3-position aldehyde group to the large vinyl-biaryl substituent resulted in an upfield shift of the H_4 singlet signal. A larger upfield shift of the H_4



Scheme 100: Attempted synthesis of a biaryl-extended quinoline derivative via Horner-Emmons reaction. Product could not be isolated from mixture.



Scheme 101: Synthesis of biaryl-extended quinoline derivatives **146c** and **147c** via a Horner-Emmons reaction.

signal was observed for the *Z*-isomer products due to the closer proximity of the large biaryl group. HRMS data for the products was consistent with the target alkene products, with distinctive isotopic masses showing the 2-position chloro substituent was retained, in contrast to the products of the attempted reaction to make **147c** from Suzuki coupling of **145c** in the pathway attempted previously. While 2D NMR experiments were more difficult to interpret for the mixture of isomers in each case, small samples of pure *E*-isomer products were obtained by column chromatography for both **146c** and **147c**, and 2D NMR experiments were used to confirm connectivity of the aromatic rings in the desired structure after the sequence of carbon-carbon bond forming reactions (Figure 86).

4.2.2 Synthesis of biaryl-extended 2-chloroquinoline derivatives

Using the same method, the remaining biaryl-extended 2-chloroquinoline derivative were also prepared. The bromobenzylphosphonate derivatives **36(k,l,m)** were reacted via a Suzuki reaction with the arylboronic acids to give the range of biaryl phosphonates **156**, **157**, **158**, and **159** (Scheme 102). In each case the corresponding biaryl products were synthesised and

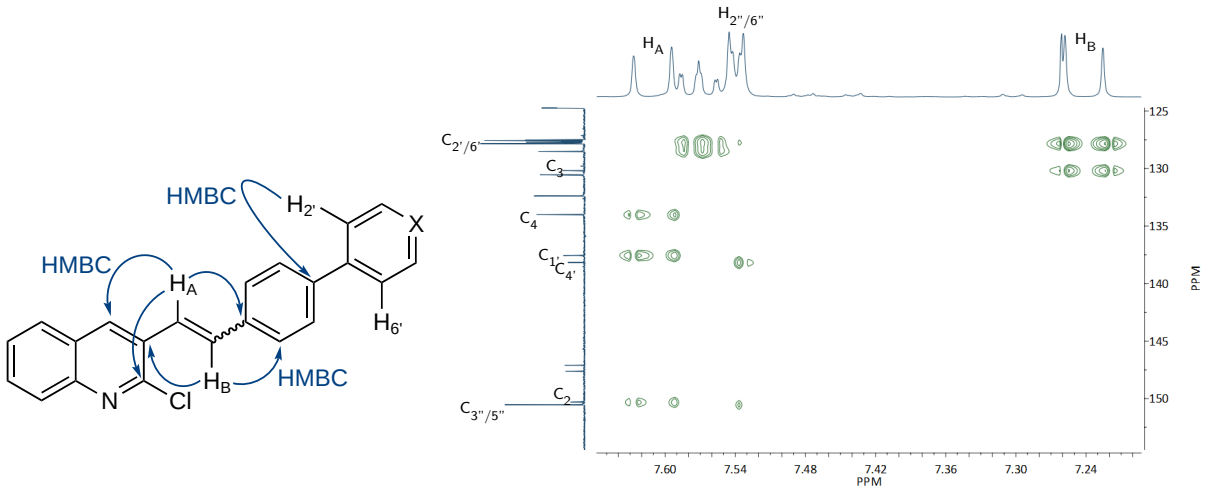
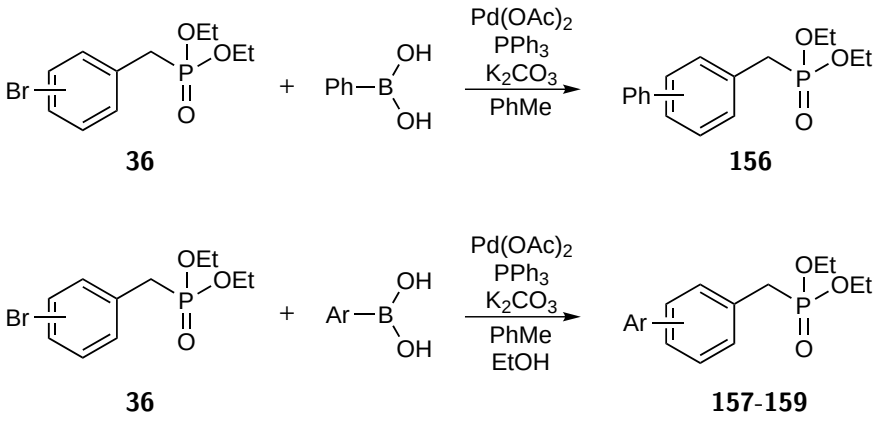


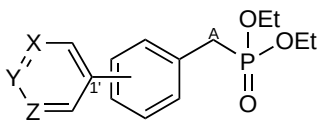
Figure 86: Sample HMBC correlations observed for both Horner-Emmons reaction products **146c** (X = C) and **147c** (X = N), demonstrating success of the sequence of carbon-carbon bond forming reactions to make the target scaffold of the target molecules. Example HMBC spectrum is for *E*-isomer of **147c** (X = N).

purified by column chromatography, with generally high yields (Table 32). In each case, there was an increase in the integration and the number of ^{1}H and ^{13}C NMR signals compared to the bromo-substituted reagents, consistent with the extended biaryl structure of the desired products.



Scheme 102: Synthesis of biaryl-extended phosphonate derivatives via Suzuki reaction. Ar = 4-pyridinyl (**157**), 3-pyridinyl (**158**), or 5-pyrimidinyl (**159**).

Table 32: Results of Suzuki reactions to yield biaryl-extended diethyl phosphonate derivatives, with key coupling constants for doublet signals.

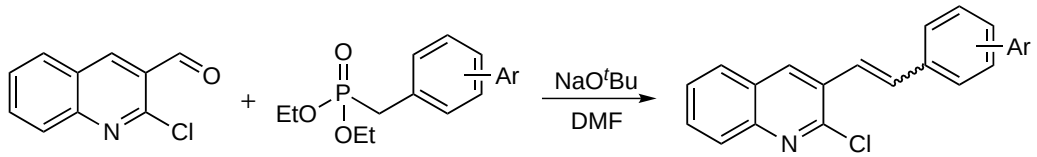


156 X, Y, Z = C
157 Y = N ; X, Z = C
158 X = N ; Y, Z = C
159 X, Z = N ; Y = C

	Yield (%)	δ_H H_A (ppm)	$^2J_{H,P}$ (Hz)	δ_C $C_{1'}$ (ppm)	$J_{C,P}$ (Hz)
156a:	89	3.18	22.2	141.2	$^4J = 0.9$
156b:	87	3.22	21.6	141.0	-
156c:	90	3.19	21.7	140.8	$^6J = 1.5$
157a:	90	3.13	22.3	149.1	$^4J = 1.6$
157b:	91	3.23	21.7	148.12	-
157c:	97	3.21	21.8	147.9	$^6J = 1.5$
158a:	96	3.12	22.3	136.9	$^4J = 1.0$
158b:	68	3.23	21.7	136.4	-
158c:	59	3.21	21.7	136.3	$^6J = 1.4$
159a:	89	3.10	22.3	134.8	$^4J = 1.6$
159b:	71	3.24	21.7	134.1	-
159c:	94	3.22	21.9	134.0	$^6J = 1.5$

For the 2- and 4-aryl substituted products, the corresponding ^4J or ^6J phosphorous-carbon coupling to the $C_{1'}$ carbon was evident as these ^{13}C NMR signals appeared as doublets. For the 2-substituted products an upfield shift of the characteristic PCH_2 doublet signal was observed in the ^1H NMR spectrum, and for the other derivatives a highly consistent downfield shift was observed compared to the corresponding bromo-substituted reagents.

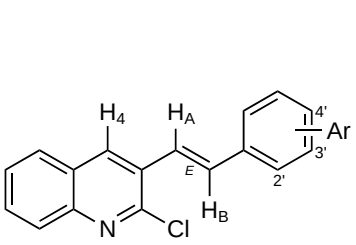
The previous experiments had effectively demonstrated that the success of the Horner-Emmons reaction of biarylphosphonates with the quinoline **144** was dependant upon the base and solvent, and some Horner-Emmons reaction conditions may instead promote formation of the quinolinol side-product and give poor yields of the desired alkene product. Given these results, the synthesis of the remaining 3-position extended quinoline derivatives via a Horner-Emmons reaction utilised sodium *tert*-butoxide as the base and DMF as the solvent, and gave generally good yields of the alkene products (Scheme 103, Table 33).

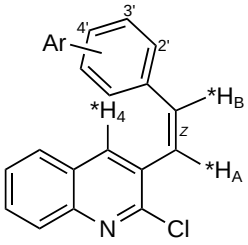


144 **36(k-m)** **146-149**

Scheme 103: Synthesis of biaryl-extended 2-chloroquinoline derivatives via Horner-Emmons reaction. Ar = Ph (**146**), 4-pyridinyl (**147**), 3-pyridinyl (**148**), or 5-pyrimidinyl (**149**).

Table 33: Results of Horner-Emmons reactions with biaryl-extended diethyl phosphonate derivatives to give 2-chloroquinoline products. Ratio of alkene products determined by ^{1}H NMR integration, usually comparison of H_4 to $*H_A/*H_B$ as these were typically isolated signals. All chemical shifts are reported in units of ppm downfield of TMS signal. * Denotes *Z*-isomer.



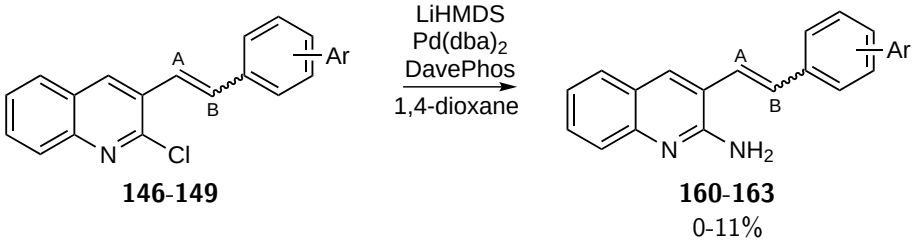


				***E*-isomer**			***Z*-isomer**		
	Ar position	**Yield (%)**	***E*:*Z* ratio**	**δ_H H_A,H_B**	**$^3J_{trans}$ (Hz)**	**δ_H H_4**	**δ_H $*H_A$,$*H_B$**	**$^3J_{cis}$ (Hz)**	**δ_H $*H_4$**
146a:	2'	78	2:1	7.46,7.18	16.2	8.07	6.69,6.79	12.1	7.86
146b:	3'	72	2:1	7.60,7.27	16.1	8.41	6.79,6.92	12.1	8.00
146c:	4'	78	5:2	7.57,7.23	16.2	8.39	6.75,6.88	12.1	8.03
147a:	2'	62	5:1	7.49,7.09	16.1	8.09	6.76,6.79	12.1	7.79
147b:	3'	64	3:1	7.60,7.26	16.1	8.40	6.83,6.92	12.1	8.00
147c:	4'	100	4:1	7.61,7.24	16.2	8.41	6.81,6.89	12.1	8.01
148a:	2'	93	5:2	7.49,7.09	16.1	8.10	6.74,6.81	12.0	7.78
148b:	3'	86	10:1	7.61,7.28	16.2	8.42	6.83,6.93	12.1	7.84
148c:	4'	78	4:1	7.58,7.23	16.2	8.39	6.79,6.89	12.1	8.00
149a:	2'	54	3:1	7.52,7.05	16.0	8.13	6.79,6.84	12.0	7.70
149b:	3'	100	3:1	7.60,7.26	16.2	8.40	6.85,6.92	12.1	8.01
149c:	4'	78	7:2	7.59,7.22	16.2	8.38	6.83,6.90	12.1	7.99

In each reaction, none of the quinolinol product **152** was observed in either the crude reaction mixture or in separated fractions after column chromatography, demonstrating that this method with specific Horner-Emmons reaction conditions can be applied more generally while avoiding the undesired side-reaction. The presence of both *E*- and *Z*-isomers of the desired products could be observed in the ^{1}H NMR spectra of the product mixture and therefore the NMR signals corresponding to each isomer could be distinguished and assigned based upon the relative magnitude of the $^{3}J_{cis}$ and $^{3}J_{trans}$ coupling constants, which were typically 12 Hz and 16 Hz respectively. The *E*-isomer was the major product for each product of **146**-**149** and in most cases a pure sample could be obtained for characterisation of the product. The *Z*-isomer was also obtained in significant enough quantities for observation of the alkene hydrogen peaks in the ^{1}H NMR spectrum as they always appeared isolated upfield of other alkenyl hydrogen peaks, although in many cases this minor isomer product could not be isolated and fully characterised. For each product the use of 2D NMR experiments definitively showed that the vinyl substituent was attached at the 3-position of the quinoline ring, and HRMS analysis of the products found signals corresponding to the desired products with a 3:1 ratio of peaks consistent with the expected ratio of chlorine isotopic abundances for the 2-chloroquinoline product.

4.2.3 Synthesis of 3-position extended 2-aminoquinoline derivatives via Buchwald-Hartwig amination

As hydrogenation under standard conditions was previously reported to result in hydrogenolysis of the aryl chloride bond for similar derivatives,[56] the proposed method in this project instead involved synthesis of the 2-aminoquinolines via a Buchwald-Hartwig amination prior to a hydrogenation step to reduce the alkene bond. To achieve this, the same conditions utilised for synthesis of the 6-position extended 2-aminoquinolines previously was also applied to the attempted synthesis of these 3-position extended biaryl derivatives (Scheme 104, compared to Scheme 62 previously).



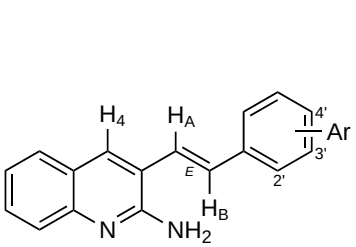
146-**149** **160**-**163**
0-11%

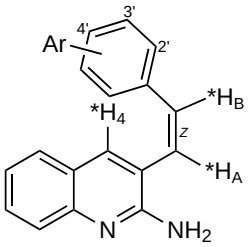
Scheme 104: Attempted synthesis of 3-position extended 2-aminoquinoline derivatives via Buchwald-Hartwig amination.

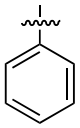
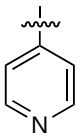
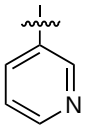
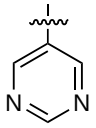
For the 3-position extended 2-chloroquinoline compounds, however, the attempted Buchwald-Hartwig aminations with LiHMDS were not found to be effective (Table 34). In each case a

complex mixture of products was produced under the sealed tube reaction conditions, and in the majority of cases the presence of any 2-aminoquinoline product was not evident using ^{1}H NMR analysis of the crude mixture.

Table 34: Yields of 3-position extended 2-aminoquinoline derivatives from Buchwald-Hartwig amination.





		Ar position	Yield (%)	*E*-isomer δ_H H_A,H_B	*E*-isomer $^3J_{trans}$ (Hz)	*E*-isomer δ_H H_4	*Z*-isomer δ_H $*H_A$,$*H_B$	*Z*-isomer $^3J_{cis}$ (Hz)
	**160a:**	2'	-[a]					
	160b:	3'	-[a]					
	160c:	4'	-[a]					
	**161a:**	2'	-[a]					
	161b:	3'	-[a]					
	161c:	4'	<5%[b]	-[c]	-[c]	8.06	6.63,6.87	12.6
	**162a:**	2'	-[a]					
	162b:	3'	11	7.20,7.22	16.5	8.05	6.63,6.89	12.2
	162c:	4'	<5%[b]	7.18,7.20	16.5	8.06	6.81,6.86	12.2
	**163a:**	2'	-[a]					
	163b:	3'	<5%[b]	-[c]	-[c]	8.05	6.66,6.89	12.1
	163c:	4'	-[a]					

[a] Signals corresponding to the desired product were not evident in the ^{1}H NMR spectra of crude reaction mixtures. [b] Crude sample containing mostly the desired product was obtained by chromatographic separation, but could not be purified. [c] Could not be determined due to overlap of signals in the ^{1}H NMR spectrum.

The presence of the desired 2-aminoquinoline product was only observed in the product mixture for four of the attempted reactions, and in one case the product 2-aminoquinoline (**162b**) could be isolated. A significant upfield shift was observed for the alkene doublet signals and the H_4 singlet signal in the ^{1}H NMR spectrum, consistent with the introduction of an

electron-donating amine substituent at the 2-position. A broad 2H signal further upfield for the amino group was also present, and HRMS analysis was consistent with replacement of the chloro-subsituent with an amine. Despite the low yield of 11%, the spectroscopic data demonstrates that the conversion of a 2-chloroquinoline to a 2-aminoquinoline can still be achieved under the established Buchwald-Hartwig amination conditions. When compared to the results of the amination of 6-position extended 2-chloroquinolines (for example, Scheme 62), it is apparent the reaction conditions are not readily generalisable to the synthesis of all extended 2-aminoquinolines.

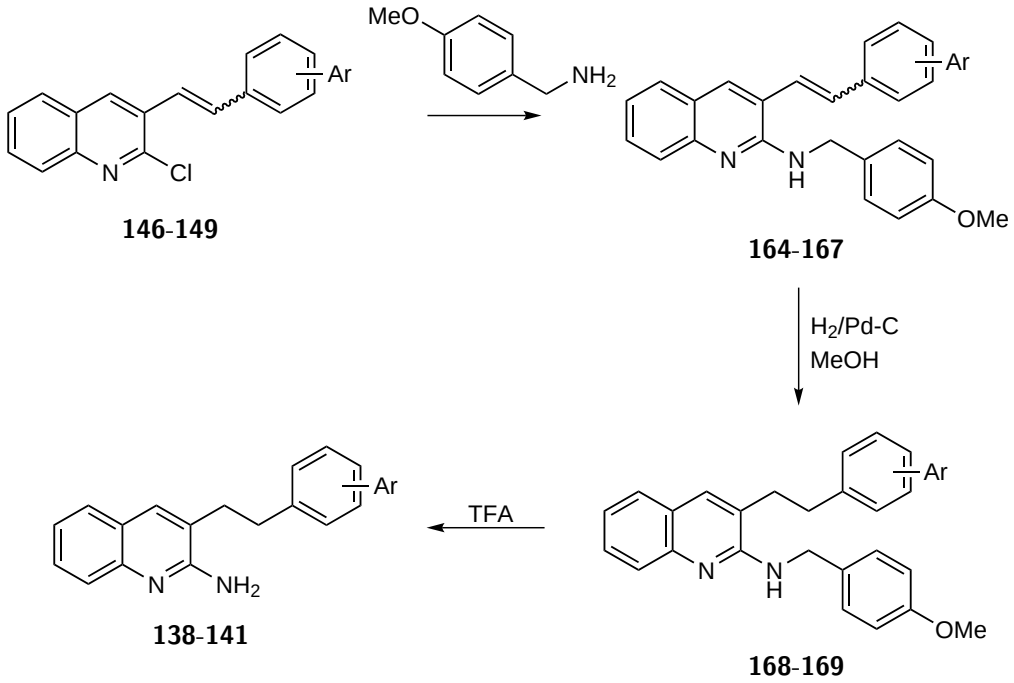
The characteristic chemical shifts of signals corresponding to the products in the ^{1}H NMR spectra were used to identify the presence of any product in the instances the reaction mixture could not be purified. Specifically, the H_4 singlet signal was typically distinctive and shifted upfield compared to the H_4 signal for the reagent, as expected due to the electron-donating amino group at the 2-position instead of the electron donating chloro-substituent. Similarly, the H_B alkene signals were generally observable as they appeared further upfield of other aromatic ^{1}H NMR signals, and for the 2-aminoquinoline product the H_B signals were shifted upfield compared to the corresponding signals in the 2-chloroquinoline reagent. The presence of a broad signal further upfield was also evident for the introduced 2-position amino group when the reaction was successful.

The excessively complex mixture of products obtained from these amination reactions was unexpected, and it was therefore suspected that the conditions used for the Buchwald-Hartwig amination resulted in degradation of the product. Alternate reaction conditions were attempted, including shorter reaction times or conducting reactions at reflux instead of in sealed pressure tubes. Similar poor and complex results were observed in each case and therefore the Buchwald-Hartwig method was not deemed a useful pathway for the 3-position extended compounds.

4.2.4 Alternate synthesis of 3-position extended 2-aminoquinoline derivatives

For a subset of derivatives, the alternate amination strategy involving substitution of the 2-position amino group first as a *para*-methoxybenyl protected amine was instead attempted (Scheme 105). The amination was achieved using the previously reported conditions, with a large excess of 4-methoxybenzylamine and high temperatures.[56]

Distillation of the excess reagent and attempted purification of the products via column chromatography gave an impure mixture of the desired product and the excess reagent 4-methoxybenzylamine, however complete separation of the amines was not possible. The impurity was not expected to affect the subsequent reactions and so the products were



Scheme 105: Alternate synthesis of biaryl-extended 2-aminoquinoline derivatives from the corresponding 2-chloroquinolines in a three-step amination procedure. Ar = Ph (**138**), 4-pyridinyl (**139**), 3-pyridinyl (**140**), or 5-pyrimidinyl (**141**).

used without further purification. In one instance, the *E*-isomer of an amination product (**165c**) was exclusively obtained by recrystallisation from dichloromethane to enable better characterisation of the product.

Similarly to the Buchwald-Hartwig amination products above (see Table 34), the products of the nucleophilic aromatic substitution reaction showed significantly upfield chemical shifts for the H_4 and alkene H_B signals in the ^{1}H NMR spectrum compared to the 2-chloroquinoline reagents due to the electron-donating amine at the 2-position instead of the chloro-substituent of the reagent (Figure 87A and 87B, Table 35). The key signals corresponding to the *para*-methoxybenzyl protected amine were also evident in the ^{1}H NMR spectra of the products. The 3H singlet peak at 3.80 ppm for the methoxy group as well as the triplet and doublet peaks corresponding to the coupled NH and benzylic CH_2 groups were particularly distinctive as these signals appeared upfield of the more complicated and overlapping signals for the aromatic and alkene hydrogen atoms. HRMS analysis also showed peaks consistent with the target structure, and the absence of the distinctive chlorine isotopic peaks for the reagents confirmed the substitution reaction had occurred at the desired position.

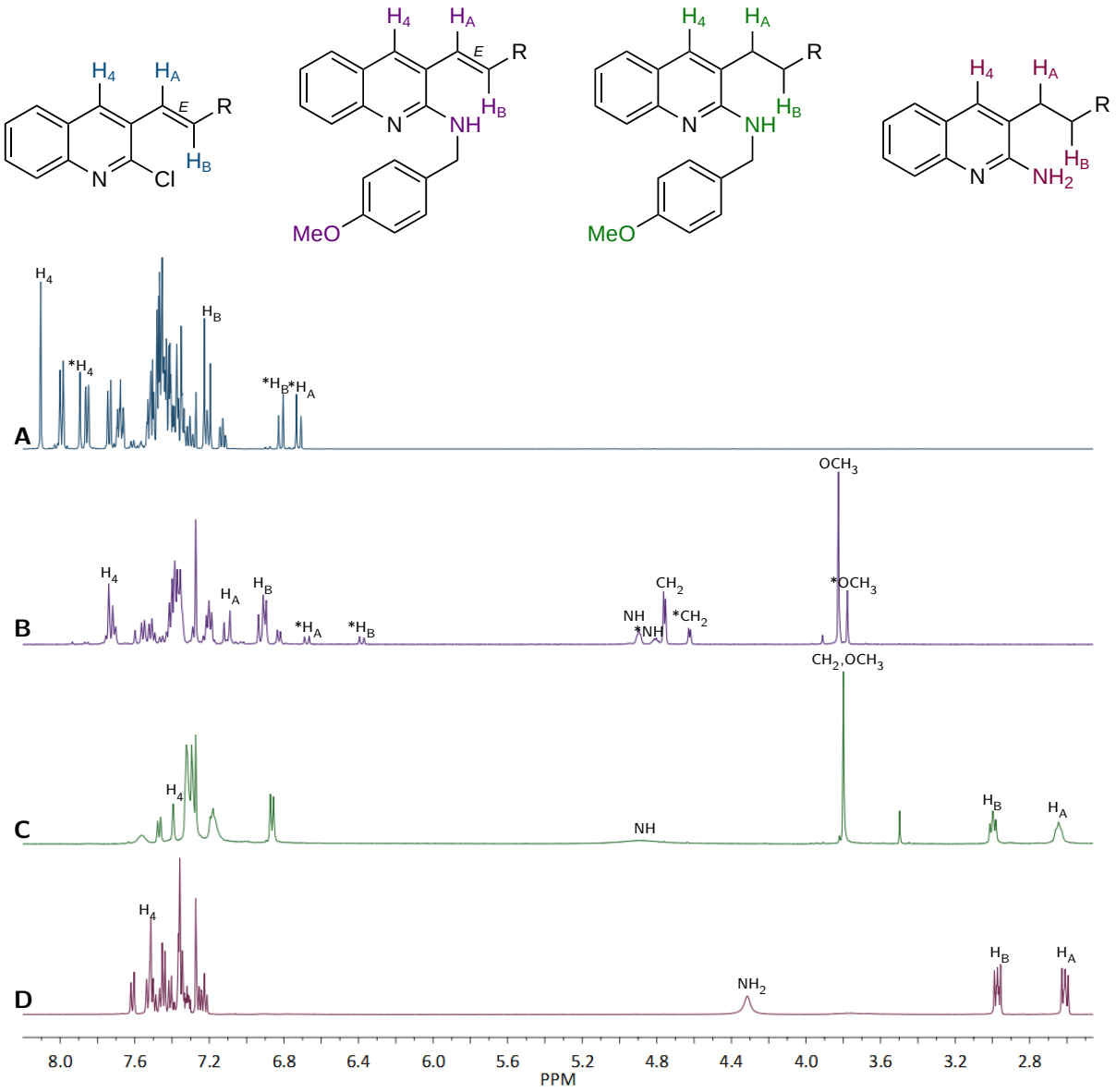
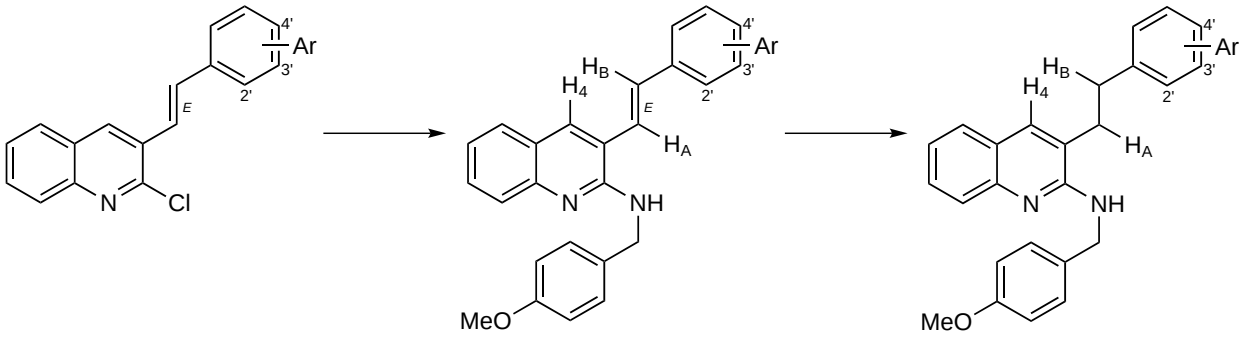
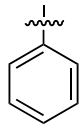
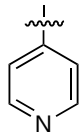
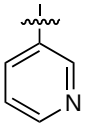
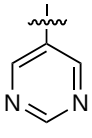


Figure 87: Comparison of ^{1}H NMR spectra for products obtained from 3-step amination procedure, to yield 3-position extended 2-aminoquinoline products. Example shown is for synthesis of biphenyl-extended compound **138a**. A: 2-Chloroquinoline reagent **146a**, B: amination product mixture containing **164a**, C: hydrogenation product mixture containing **168a**, and D: target 2-aminoquinoline compound **138a**. Only key signals are annotated, and * denotes signal corresponding to *Z*-isomer of an alkene product.

Table 35: Results of amination and hydrogenation procedure and characteristic NMR signals demonstrating successful reaction at each step. Only *E*-isomer signals with the vicinal coupling constant (in Hz) are reported for alkene products. Signals for H_A and H_B were not assigned individually due to the impure mixtures and the overlap of signals.



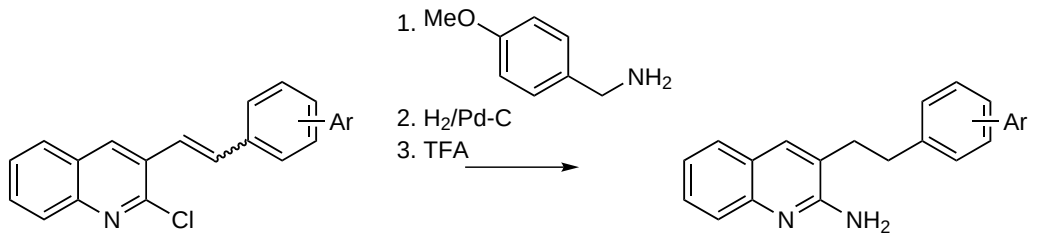
Ar group/ position		Amination				Hydrogenation		
			δ_H H_A,H_B (ppm)	$^3J_{cis}$ (Hz)	δ_H H_4 (ppm)		δ_H H_A,H_B (ppm)	δ_H H_4 (ppm)
	2'	**164a**:	6.90,7.09	15.8	7.72	**168a**:	2.63,2.98	7.38
	2'	**165a**:	6.98,7.02	15.9	7.72	**170a**:	2.67,2.98	7.40
	4'	**165c**:	7.10,7.14	16.0	7.95	**170c**:	2.84,3.08	7.62
	3'	**166b**:	7.11,7.16	15.9	7.94	**171b**:	2.87,3.09	7.63
	4'	**166c**:	7.09,7.14	15.9	7.95	**171c**:	2.82,3.05	7.61
	3'	**167b**:	7.12,7.16	15.9	7.95	**169b**:	2.86,3.11	7.72
	4'	**167c**:	7.11,7.15	16.2	7.95	**169c**:	2.95,3.08	7.61

Hydrogenation was used to reduce the alkenes **164**-**167** to give the phenethyl-substituted products **168**-**169** under standard hydrogenation conditions (Scheme 105). In some cases the reagents had low solubility in methanol, which resulted in low conversion to the desired product, and therefore in some cases a 1:1 methanol/ethanol mixture was used as the solvent and the reaction mixture was heated to 40°C to give a better conversion. The products of this step were again used without complete purification due to the difficulties in purifying amines by column chromatography.

The success of the hydrogenation reactions was clearly demonstrated using spectroscopic methods. The ^{1}H NMR spectra of the products showed that the distinctive alkene doublet signals with large coupling constants were no longer present, and instead upfield 2H triplet-like signals corresponding to the CH_2 groups in the ethylene chain were evident (Figure 87C, Table 35). The signals corresponding to the *para*-methoxybenzyl-protected amino substituent were also still present, showing that the protecting group had not been removed under the hydrogenation conditions.

Treatment of the amine-protected compounds **168**-**169** with trifluoroacetic acid removed the *para*-methoxybenzyl protecting group to achieve the target 2-aminoquinoline products **138**-**141**. The excess trifluoroacetic acid was removed by evaporation under reduced pressure, and the salt residue was treated with saturated aqueous sodium bicarbonate solution and extracted into dichloromethane, then purified by column chromatography to yield the pure free amine products, with ^{19}F NMR spectra collected to confirm that there was no residual trifluoroacetic acid present. Aside from the loss of signals corresponding to the protecting group there were only small differences in the ^{1}H and ^{13}C NMR spectra compared to the reagents. HRMS analysis showed a loss in the mass of the product consistent with the absence of the protecting group, and the integration of the broad amine signal in the ^{1}H NMR spectrum was consistent with an NH_2 group for the 2-aminoquinoline instead of the NH of the *N*-protected reagents (Figure 87D).

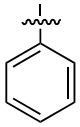
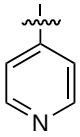
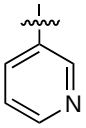
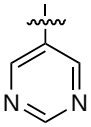
A moderate yield of the 2-aminoquinolines from 2-chloroquinolines was generally achieved over the three steps using this method (Scheme 106, Table 36). The loss of yield over during the process was likely due to the attempted purification of the amine products using column chromatography after the introduction of the *para*-methoxybenzyl protected amine at the 2-position of the quinoline ring, and some product may have also been lost in the aqueous work-up to remove the residual trifluoroacetic acid and salts in the final step of the procedure. Despite this, the procedure yielded each of the derivatives targeted in the exploratory synthesis, and therefore proved a more effective amination strategy than the attempted Buchwald-Hartwig aminations.



146-149 **138-141**
18-33%

Scheme 106: Synthesis of biaryl-extended 2-aminoquinoline derivatives from the corresponding 2-chloroquinolines in a three-step amination procedure. Ar = Ph (**138**), 4-pyridinyl (**139**), 3-pyridinyl (**140**), or 5-pyrimidinyl (**141**).

Table 36: Results of three-step amination procedure, and characteristic NMR signals demonstrating successful removal of the *para*-methoxybenzyl group.

Ar group/ position		Deprotection	δ_H H_A,H_B (ppm)	δ_H H_4 (ppm)	Overall Yield (%)
	2	**138a**:	2.59,2.96	7.50	36
	2	**139a**:	2.67,3.01	7.41	31
	4	**139c**:	2.98,3.13	7.78	33
	3	**140b**:	2.95,3.13	7.69	31
	4	**140c**:	2.95,3.12	7.70	18
	3	**141b**:	2.96,3.16	7.66	31
	4	**141c**:	2.95,3.14	7.69	32

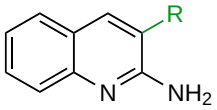
4.3 Binding studies of 3-position extended 2-aminoquinoline derivatives

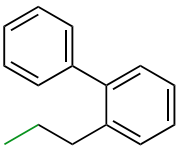
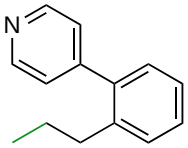
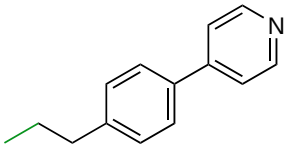
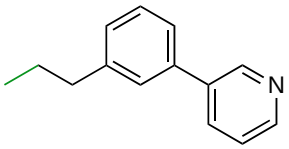
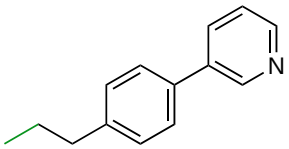
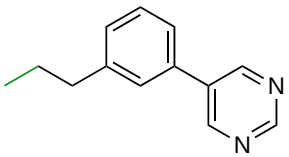
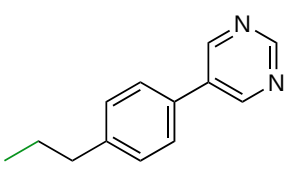
Each of the 3-position 2-aminoquinoline ligands with a biaryl substituent was tested for binding with the *murine* Tec SH3 domain using the SPR assay method (Table 37, see Section 2.4.2, page 114 for method). The previous 3-substituted quinoline lead compound **137** was also tested, but was found to be completely insoluble under the assay conditions and therefore the K_d value determined from the SPR method could not be directly compared to the value determined by the NMR chemical shift perturbation assay method.

The novel biphenyl-extended 2-aminoquinoline compound **138a** was also insoluble under the assay conditions, but the other biaryl compounds with pyridine or pyrimidine rings did appear to remain soluble. These observations demonstrate that the incorporation of heteroaromatic rings instead of benzene rings is an effective strategy for incorporation larger aromatic scaffolds while maintaining water solubility, and therefore a highly useful strategy addressing the aim of designing more drug-like small-molecule compounds compared to the previous lead compound.

While promising differences in solubility of the ligands were observed with this range of biaryl extended ligands compared to the previous 3-position extended 2-aminoquinoline lead compound **137**, unfortunately there were not any measurable differences in binding using the SPR assay method. This assay technique was not able to effectively measure the binding affinity for compound if the K_d value was higher than approximately 20 μM. The K_d reported for the lead compound **137** was $K_d = 40 \pm 8$ μM,[56] and therefore a 3- or 4-fold improvement in the binding affinity would be required for a determination of the K_d value using the SPR assay method. The results from the attempted assays showed that none of the ligands appeared to reach saturation binding with the SH3 domain for any concentration range tested, and therefore substantial improvement in the strength of the binding affinity with the Tec SH3 domain was not achieved. Due to the lack of improvement in the strength of the binding activity observed with this range of compounds, the synthesis of other 3-position biaryl-extended 2-aminoquinoline ligands was not pursued further.

Table 37: Results of SPR assays for 2-aminoquinoline ligands with a 3-position biaryl substituent.



R =	Compound	Screening K_d (μM)
	**138a**	*insoluble*
	**139a**	$> 50^a$
	**139b**	$> 50^a$
	**140a**	$> 50^a$
	**140b**	$> 50^a$
	**141a**	$> 50^a$
	**141b**	$> 50^a$

[a] Response-concentration curve not at plateau, saturation binding not achieved.

4.4 Synthesis of pyridinylethyl-extended quinoline derivatives

A similar Horner-Emmons reaction pathway as not anticipated to be an effective method for the synthesis of **142** derivatives, as the synthesis of similar pyridinylmethylidene compounds had been unsuccessfully pursued previously (e.g. compound **34c**, Scheme 40). In the previous attempted synthesis, the required pyridinylmethyl-extended phosphonate reagents could not be synthesised or isolated in sufficient quantities to make the reaction pathway feasible. As the same reagent would be required for the Horner-Emmons synthesis of **142** derivatives, this pathway was likewise not deemed feasible in the synthesis of these target compounds. The most effective method which was utilised in the previous project was the similar Wittig reaction, which is more feasible due to the achievable synthesis of the required Wittig reagents. From the results of the previous work, it was therefore expected that a synthesis from previously synthesised quinoline reagent **144** and Wittig reagents **52(a-c)** via a Wittig reaction would effectively yield the 2-chloroquinolines (**172**). Subsequently, the required 2-aminoquinolines (**142**) could be obtained via either amination to give a *N*-protected intermediate (Pathway 1, Figure 88), or via Buchwald-Harwtig amination (Pathway 2, Figure 88).

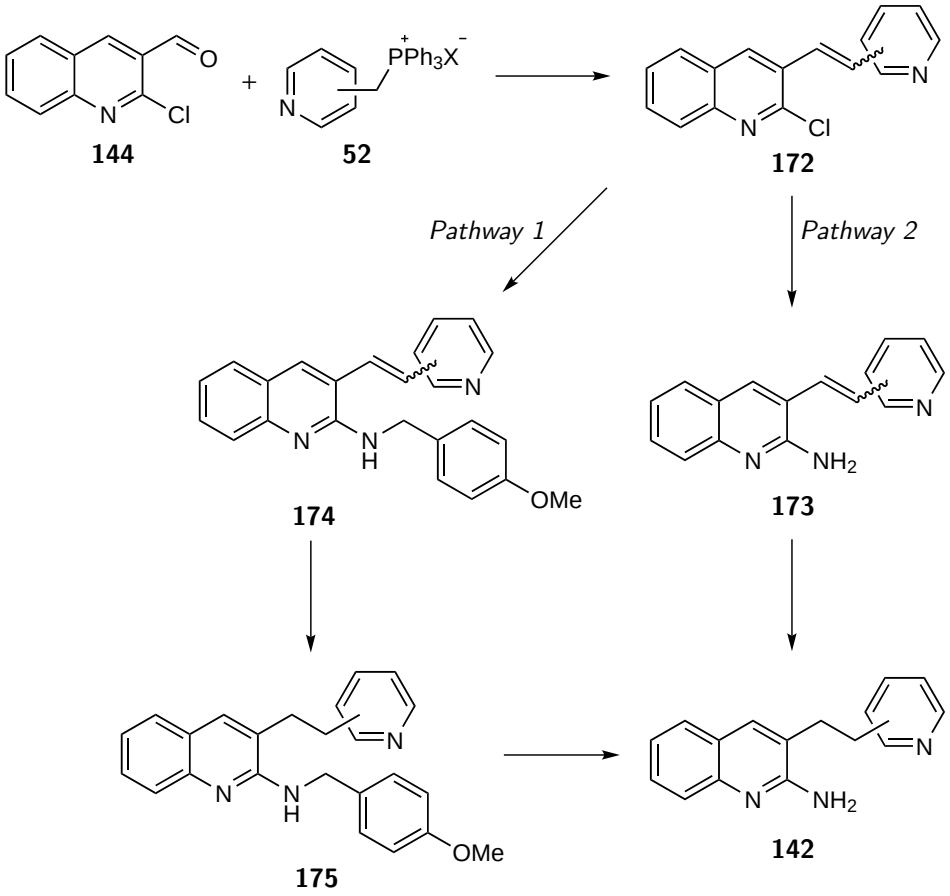
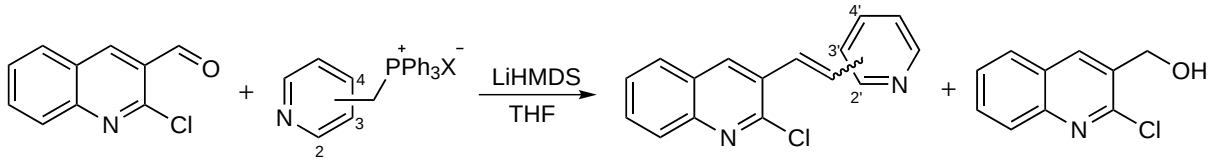


Figure 88: Proposed synthetic pathways to yield pyridinylethyl extended 2-aminoquinoline derivatives (**142**) via a Wittig reaction.

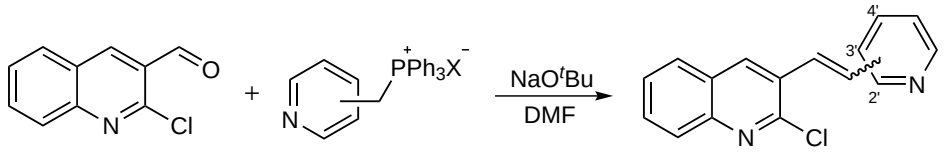
Using the same Wittig reaction conditions used for the synthesis of the substituted piperidines

50 previously, the quinoline reagent **144** was reacted with the Wittig reagents **52** using LiHMDS and THF (Scheme 107). In each case low to moderate yields of the desired products were obtained (32-52%), and signals corresponding to the quinolinol side-product **152** were observed in the ^{1}H NMR spectra of the crude reaction mixtures. Similar results had been observed in attempted Horner-Emmons reactions of **144** previously when LiHMDS and THF were used as the base and solvent, and it had been determined in that case that using sodium *tert*-butoxide and DMF had resulted in substantially improved results. The same conditions were then attempted in the Wittig reaction, and again this resulted in improved results compared to the initial reaction conditions (Scheme 108).



a: 2'-pyridinyl, 52%
b: 3'-pyridinyl, 33%
c: 4'-pyridinyl, 32%

Scheme 107: Attempted synthesis of pyridinylvinyl extended 2-chloroquinoline derivatives **172(a-c)** via Wittig reaction with LiHMDS in THF.

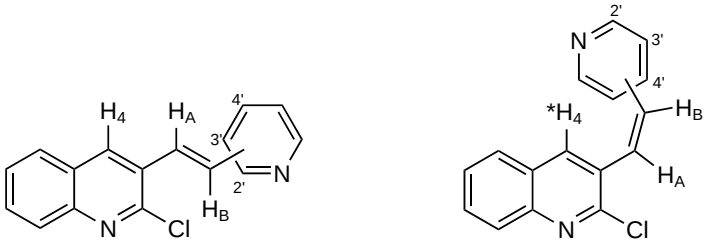


Scheme 108: Synthesis of pyridinylvinyl extended 2-chloroquinoline derivatives **172(a-c)** using modified Wittig reaction conditions.

The ^{1}H NMR spectra of the isolated products showed substantial differences in the isomer selectivity of the reaction (Table 38). The signals corresponding to each alkene isomer of the products **172b** and **172c** could be assigned as both isomers of the product were present. The alkene signals for the *Z*-isomer appeared further upfield of the other signals, and had a smaller coupling constant of approximately 12 Hz, whereas the larger coupling constant of the *E*-alkene signals was typically 16 Hz. 2D NMR experiments were used in each case to demonstrate that the desired carbon-carbon bond-forming reaction had occurred to give the 3-position pyridinylvinyl quinoline product. For the 3-pyridine and 4-pyridine derivatives (**172b** and **172c** respectively) the product was almost exclusively produced as the *Z*-isomer. In contrast, for the 2-pyridine product **172a** only one isomer was obtained, and the large alkene coupling constant of 16.1 Hz indicated that the product was only present as the *E*-isomer. None of the *Z*-isomer was observed in the NMR spectra of the crude mixture or the column fractions after purification. Syntheses of these compounds had not been published previously,

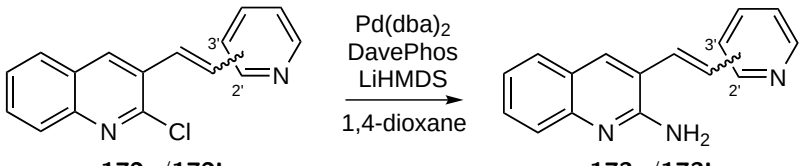
and data used to determine the distribution of product isomers for similar reported Wittig reactions was not available. Further investigation into reactions of pyridinylmethyl-extended Wittig reagents with aldehydes would be necessary to explain the differences in alkene isomer selectivity observed in these Wittig reactions.

Table 38: Results of Wittig reactions to give pyridinylvinyl-extended 2-chloroquinoline products **172**. Ratio of alkene products determined by ^{1}H NMR integration, usually comparison of H_4 to $*H_A/*H_B$ as these were typically isolated peaks. Chemical shifts are reported in units of ppm downfield of TMS.



				***E*-isomer**			***Z*-isomer**		
	Pyridinyl position	**Yield (%)**	***E*:*Z* ratio**	**δ_H H_A,H_B**	**$^3J_{trans}$ (Hz)**	**δ_H H_4**	**δ_H $*H_A$,$*H_B$**	**$^3J_{cis}$ (Hz)**	**δ_H $*H_4$**
172a:	2'	81	1:0	8.03,7.28	16.1	8.42	-	-	-
172b:	3'	69	1:99	7.59,7.17	16.3	8.48	6.89,6.83	12.1	7.89
172c:	4'	45	1:20	7.73,7.12	16.2	8.41	6.96,6.80	12.2	7.87

The Buchwald-Hartwig amination to give the 2-aminoquinoline product was attempted, and in two cases the desired products **173a** and **173b** were successfully synthesised and isolated, although with low yields (Scheme 109). Spectroscopic methods were used to determine that the isolated products were the desired 2-aminoquinoline products. In the ^{1}H NMR spectra of the products a broad signal with integration corresponding to two hydrogen atoms was present, consistent with the introduced 2-position amino group (Figure 89B). Upfield shifts of the H_4 signal and H_B alkene signal compared to the reagent were also consistent with the introduction of the electron-donating amino substituent at the 2-position instead of the chloro substituent of the reagent (Figure 89A). HRMS analysis of the products also showed a reduction in the mass found which was consistent with the product, and the 3:1 peaks observed for the reagents due to the presence of the chloro substitent were no longer present.



172a/172b **173a/173b**

Scheme 109: Synthesis of pyridinylvinyl extended 2-aminoquinoline derivatives via Buchwald-Hartwig amination.

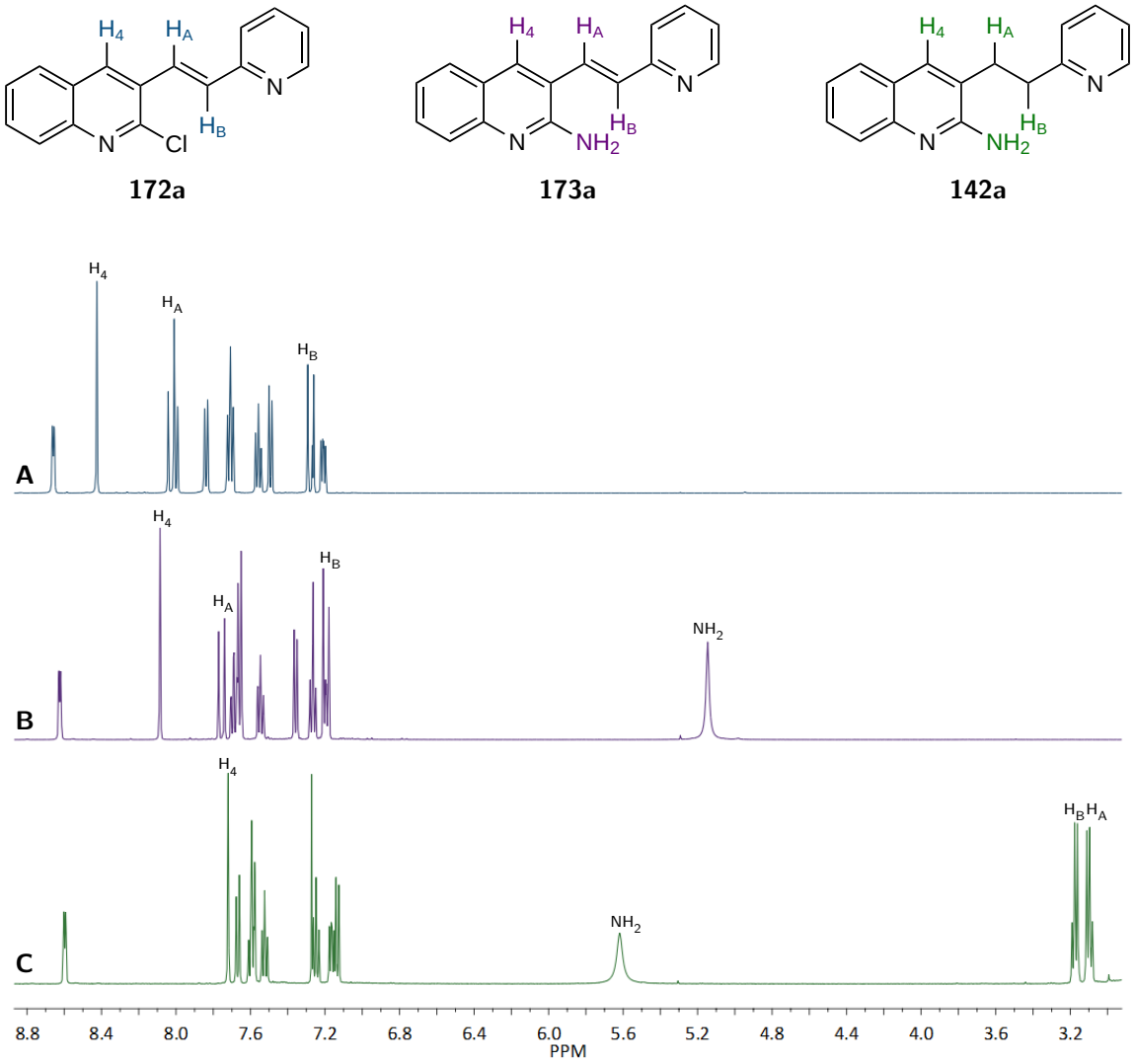
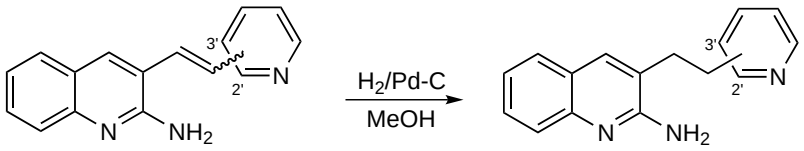


Figure 89: Comparison of ^{1}H NMR spectra for synthesis of 2-aminoquinolines **142** via Buchwald-Hartwig reaction pathway. Spectra shown are for synthesis of compound **142a**. A: 2-Chloroquinoline reagent **172a**, B: product of Buchwald-Hartwig amination **173a**, and C: target 2-aminoquinoline compound **142a**.

From the available pyridinyl-extended 2-aminoquinoline compounds **173a** and **173b**, a hydrogenation reaction under standard conditions reduced the alkene bond formed in the Wittig reaction to give the target compounds **142a** and **142b** in quantitative yield (Scheme 110). HRMS analysis of the isolated products showed a mass increase consistent with two hydrogen atoms, and the alkene doublet signals with large coupling constants in the ^{1}H NMR spectra were no longer present (Figure 89C). A pair of strongly coupled 2H signals was present upfield in the ^{1}H NMR spectra of the products instead, and 2D NMR experiments were used to demonstrate that these signals correspond to an ethylene bridge attaching the pyridine ring to the 3-position of the aminoquinoline.

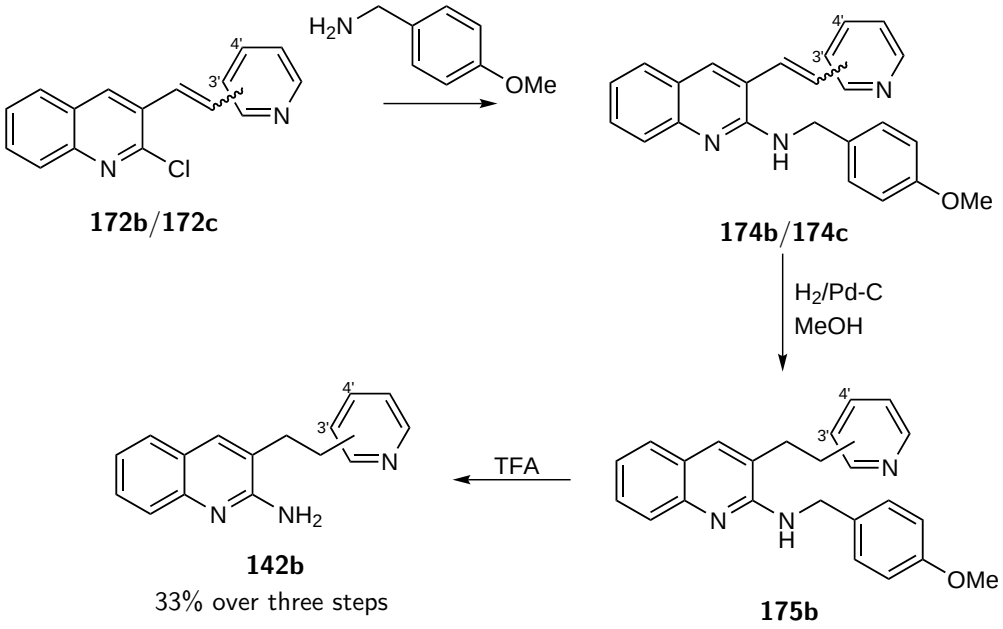
One of the desired 2-aminoquinoline compounds (**173c**) could not be synthesised using the Buchwald-Hartwig procedure, which was low yielding for all derivatives, and instead the three-step amination process using *para*-methoxybenzylamine was investigated (Scheme 111). In the



173a/173b **142a/142b**

Scheme 110: Synthesis of pyridinylethyl extended 2-aminoquinoline derivatives via hydrogenation reaction.

first step of the procedure, the 2-chloroquinolines **172b** and **172c** synthesised via the Wittig reaction were treated with *para*-methoxybenzylamine at high temperatures. The desired 2-position substituted products **174b** and **174c** were not completely purified but the ^{1}H NMR data was used to demonstrate that the desired products were obtained in each case, with distinctive upfield signals observed for the *para*-methoxybenzyl group and, compared to the 2-chloroquinoline reagent, upfield shifts of quinoline ring signals consistent with replacement of the chloro-substituent with the amine group.



172b/172c

174b/174c

142b
33% over three steps

175b

Scheme 111: Attempted synthesis of pyridinylethyl extended 2-aminoquinoline derivatives **142b** and **142c** via three-step amination procedure.

The recovery of **174c** from the amination reaction and partial purification by column chromatography was very low (<15%) and insufficient for the remaining steps of the synthetic procedure. For the 3-pyridine derivative (**174b**) the nucleophilic aromatic substitution reaction was followed by hydrogenation of the alkene bond formed in the Wittig reaction under standard conditions. Again, loss of the distinctive alkene doublet signals in the ^{1}H NMR spectra confirmed that the reduction had proceeded successfully. The appearance of two upfield signals corresponding to the ethylene bridge also confirmed the desired products **175b** and **175c** had been formed, and the signals corresponding to the *para*-methoxybenzyl group showed the *N*-protecting group was still present.

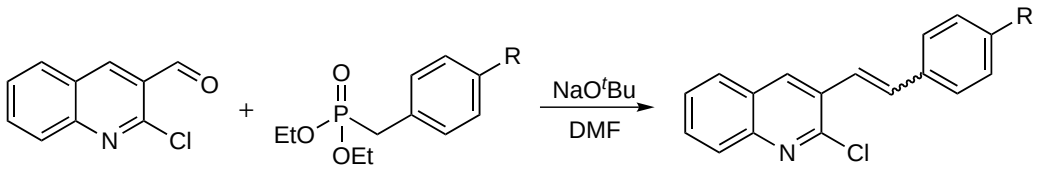
The final step was removal of the *para*-methoxybenzyl group by treatment with trifluoroacetic acid. The 3-pyridine product **142b** had previously been made via the Buchwald-Hartwig amination pathway, and the spectroscopic data collected for the product via the *N*-protected pathway was found to be directly comparable to the previously obtained data. For the products obtained by trifluoroacetic acid removal of the *para*-methoxybenzyl group, the HRMS data was consistent with loss of the amine-protecting group, and the signals corresponding to the *para*-methoxybenzyl group were not observed in the NMR spectra of the products, confirming the desired reaction had occurred.

The yield of the 2-aminoquinolines obtained from the 2-chloroquinolines via this three step method was higher than via the Buchwald-Hartwig pathway (33% c.f. 7% for synthesis of **142b** respectively). It was suspected that the Buchwald-Hartwig amination conditions resulted in significant degradation of the quinoline compounds present, resulting in the low yield of the desired product by the first method. In contrast, the low yield via the *para*-methoxybenzyl protected pathway was due to the substantial solubility of the product in the aqueous layer during liquid-liquid extraction in the work-up procedure, and therefore a significant amount of the product was not recovered. Ideally, a synthetic pathway using Buchwald-Hartwig amination conditions which do not cause degradation of the 3-position extended quinoline compounds would likely result in the highest yield, but effective conditions were not identified during this project.

4.5 Synthesis of simple 3-phenethyl-extended quinoline derivatives

The synthetic methods developed for the 3-position biaryl-extended quinoline ligands were readily adapted to make the simpler target ligands **143a** and **143b**. The same Horner-Emmons synthetic pathway was used due to the similar but simpler structure of these target ligands compared to the biaryl compounds, requiring a shorter four step synthetic pathway.

The required phosphonate derivatives **36p** and **36s** had already been synthesised for a previous section of this project (see Chapter 2). These were reacted in a Horner-Emmons reaction with the quinoline reagent **144**, using sodium *tert*-butoxide as the base in DMF, which were the conditions found to be most effective in the synthesis of the similar compound **145c** (Scheme 112). The reaction gave good yields of the desired products **176a** and **176b**, which were obtained predominantly as the *E*-isomer (Table 39). Spectroscopic results were consistent with the 2-chloroquinoline products isolated previously, in particular the characteristic alkene doublet peaks observed in the ^{1}H NMR spectrum which were used to determine the ratio of product isomers.



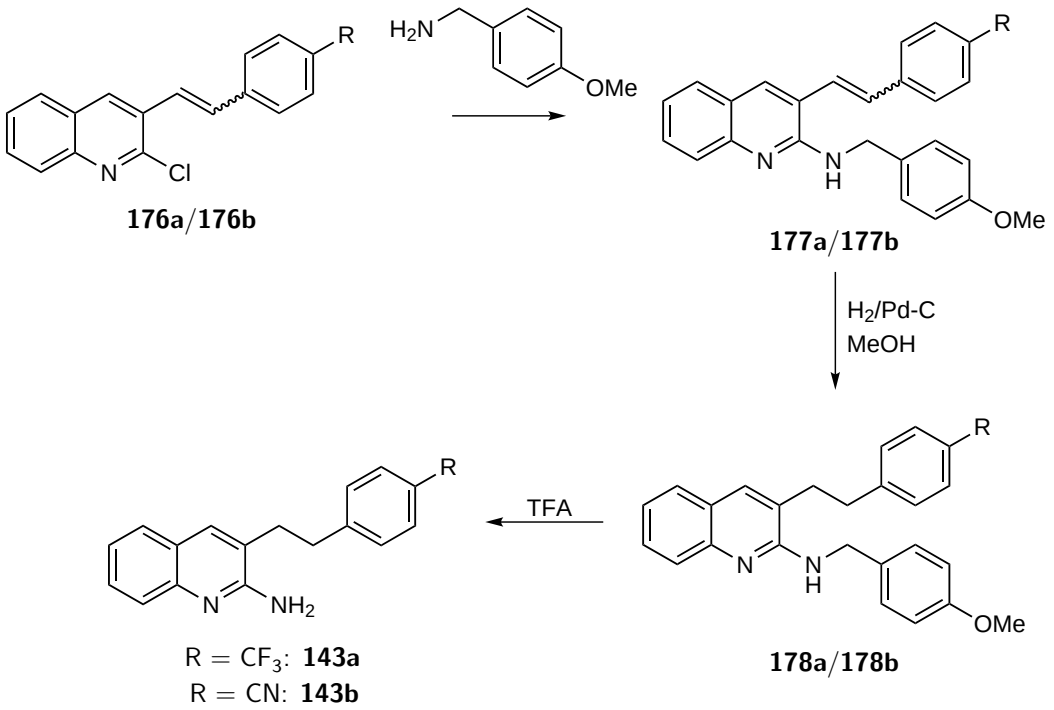
R = CF_3: **176a**, 72%
R = CN: **176b**, 69%

Scheme 112: Horner-Emmons synthesis of simple phenethyl extended 2-chloroquinoline derivatives **176a** and **176b**.

Table 39: Results of Horner-Emmons reactions with diethyl benzylphosphonate derivatives, to give 3-position extended 2-chloroquinoline products. Ratio of alkene products determined by ^{1}H NMR integration, usually comparison of H_4 to $*H_A/*H_B$ as these were typically isolated signals. * denotes *Z*-isomer.

				***E*-isomer**			***Z*-isomer**		
	R	**Yield (%)**	***E*:*Z* ratio**	δ_H **H_A,H_B**	$^3J_{trans}$ **(Hz)**	δ_H **H_4**	δ_H **$*H_A$,$*H_B$**	$^3J_{cis}$ **(Hz)**	δ_H **$*H_4$**
176a:	CF_3	72	3:1	7.61,7.21	16.2	8.39	6.88,6.86	12.9	7.87
176b:	CN	69	2:1	7.64,7.19	16.2	8.40	6.91,6.85	12.2	7.70

The three step amination procedure via a *para*-methoxybenzyl protected intermediate was then used to give the products **177a** and **177b** (Scheme 113). Characteristic changes in the spectroscopic data was used at each step to demonstrate successful reaction (Tables 40, 41), as described for the biaryl derivatives previously.



R = CF_3: **143a**
R = CN: **143b**

Scheme 113: Procedure for conversion of 2-chloroquinolines **176a** and **176b** to 2-aminoquinolines **143a** and **143b** via three step amination method.

Table 40: Results of amination and hydrogenation procedure for simple 3-position phenethyl-extended 2-aminoquinolines, and characteristic NMR signals demonstrating successful reaction at each step. Only *E*-isomer signals with the vicinal coupling constant are reported for alkene products. Signals for H_A and H_B were not assigned individually due to the impure mixtures and the overlap of signals.

	Amination				Hydrogenation		
R =		**δ_H H_A,H_B (ppm)**	**($^3J_{cis}$) (Hz)**	**δ_H H_4 (ppm)**		**δ_H H_A,H_B (ppm)**	**δ_H H_4 (ppm)**
CF_3	**177a:**	7.10,7.13	16.3	7.94	**178a**	2.81,3.08	7.58
CN	**177b:**	7.08,7.11	16.0	7.94	**178b**	2.80,3.06	7.52

Table 41: Results of 3-step amination procedure, and characteristic NMR signals demonstrating successful removal of the *para*-methoxybenzyl group.

	Deprotection			
R =		**δ_H H_A,H_B (ppm)**	**δ_H H_4 (ppm)**	**Overall Yield (%)**
CF_3	**143a:**	2.90,3.11	7.63	53
CN	**143b:**	2.90,3.12	7.59	49

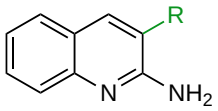
Spectroscopic methods were used to demonstrate that the desired products **143a** and **143b** had been synthesised and isolated in each case. The HRMS peaks for each product were consistent with the expected structures, and the ^{1}H NMR spectra did not show alkene doublet signals with large coupling constants or signals corresponding to the *para*-methoxybenzyl group. Two upfield signals for the ethylene linker chain were observed, and 2D NMR experiments were used to demonstrate that these signals had correlations to the substituted benzyl group and to the quinoline ring consistent with a 3-position phenethyl-substituted quinoline structure.

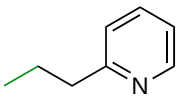
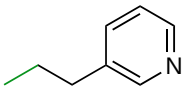
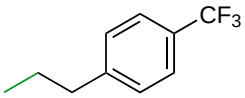
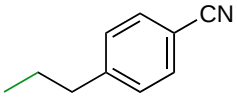
4.6 Binding studies of simple 3-position extended 2-aminoquinoline derivatives

The simple 3-position extended 2-aminoquinoline ligands were also assayed with the Tec SH3 Domain using the SPR assay method, to investigate whether substantial improvements in the strength of the binding interaction had been achieved (Table 42).

One of the ligands, **143a**, was insoluble under the assay conditions. The other compounds contained an additional pyridine ring or the more hydrophilic amide substituent, and therefore had sufficient aqueous solubility for the SPR assay method and could be tested for binding affinity with the Tec SH3 domain. Even though they appeared to remain soluble under the assay conditions, however, none of the 3-position extended 2-aminoquinolines appeared to reach saturation binding of the Tec SH3 domain target under the concentrations tested. From

Table 42: Results of SPR assays for simple 2-aminoquinoline ligands with a 3-position phenethyl-type substituent.



R =	Compound	Screening K_d (μM)
	**142a**	$> 50^a$
	**142b**	$> 50^a$
	**143a**	*insoluble*
	**143b**	$> 50^a$

[a] Response-concentration curve not at plateau, saturation binding not achieved.

the collected data it was therefore apparent that the tested ligands did not have a sufficiently strong binding interaction with the protein target to enable determination of the K_d value using the SPR assay method. Based upon these results, any difference or improvement in the strength of the binding interaction of these ligands could not be ascertained.

5 Conclusions and Future Directions

5.1 6-Position extended 2-aminoquinoline ligands

A large range of 6-position extended 2-aminoquinoline derivatives were synthesised and the binding affinity with the *murine* Tec SH3 domain was investigated using the SPR method. The assayed compounds were based upon the 4-benzylpiperidine extended compound which was previously the strongest binding small-molecule ligand for the Tec SH3 domain. The range of compounds prepared varied in size, scaffold, functional groups, and hydrophilicity, and were all prepared according to a similar general procedure. The synthesis methodology developed was widely generalisable to yield the majority of the target compounds, showing the versatility of the process.

Several of the compounds bound with stronger binding affinity than the previous lead compound. The strongest binding ligands varied in scaffold, size, and functional groups (Figure 90), which indicated that a range of different factors were tolerated upon binding to the Tec SH3 domain. These compounds are the strongest binding small-molecule ligands for a SH3 domain identified to date.

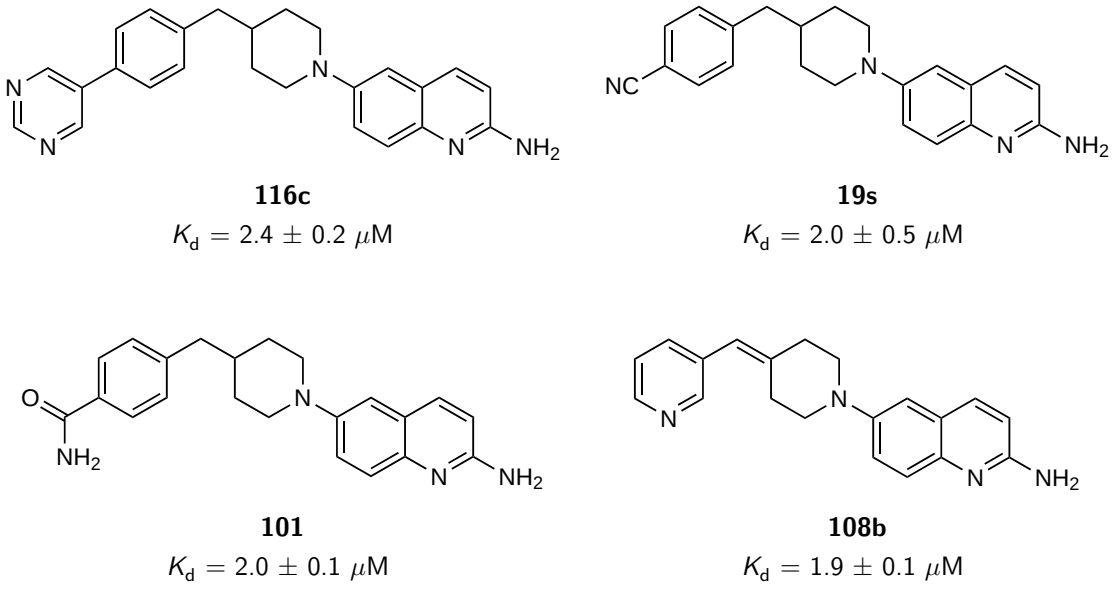


Figure 90: 6-Position extended 2-aminoquinoline derivatives with strongest binding affinity for the Tec SH3 domain, as determined by the SPR assay method.

In addition to the improved binding affinity, these compounds all included additional hydrophilic functional groups (**101** and **19s**) or contained pyridine rings replacing benzene rings in the previously reported compounds (**23b** and **116c**). The previous studies had identified that a benzyl group in the 6-position quinoline substituent improved the binding affinity, but in this work it was found that electron poor benzene rings resulted in a further improvement in the

strength of the binding interaction, whether it was due to the comparatively electron poor pyridine ring, or by addition of an electron-withdrawing substituent. Addition of even the largest 6-position substituents with biaryl groups was found to be tolerated, and a range of substituent shapes were also tolerated, which potentially indicates that there is substantial space to accommodate further extensions without causing steric clashes with the protein structure.

Most importantly, it was found that significant improvements in binding affinity could be achieved while still reducing the overall hydrophobicity of the ligand. One of the most significant challenges of designing inhibitors for protein-protein interaction surfaces are the largely flat and hydrophobic binding surfaces which are typical of these targets, for which structure-based design typically leads to large and lipophilic ligand compounds with poor water solubility. From the success of the design strategies employed in this work, the incorporation of pyridine rings and hydrophilic functional groups may be a useful and broadly applicable to improve the drug-like characteristics of some inhibitors without compromising the strength of the binding interaction.

5.2 3-Position extended 2-aminoquinoline ligands

A range of 3-position extended 2-aminoquinoline derivatives were prepared to further explore promising results in previous studies, which identified a potential favourable binding interaction. While a range of the target compounds were successfully prepared via a series of general synthetic procedures, no substantial improvement in binding affinity could be measured using the SPR assay method, as the range of concentrations which could be tested did not indicate a substantial interaction of the ligands with the Tec SH3 domain target.

The previously reported compound which identified the additional binding interaction was insoluble under the SPR assay conditions, so no comparison or indication of the binding affinity could be made. In contrast to this compound, however, the majority of the 3-position extended 2-aminoquinoline derivatives prepared in this work did appear to be soluble under the assay conditions, which would indicate that aqueous solubility of the compounds was somewhat improved. While this does address the aim of reducing the overall hydrophobic character of the ligand and improving the drug-like characteristics of the tested compounds, a very significant improvement in the strength of the binding interactions with the Tec SH3 domain would be required before the 3-position extended compounds might be considered as 'effective' ligands for the Tec SH3 domain. From the results of this work, however, no progress was made into designing ligands which could better access the additional favourable binding interaction.

5.3 Development of extended 2-aminoquinoline ligands for the Tec SH3 Domain

A lack of substantial improvement in binding affinity was observed for the range of novel 3-position extended 2-aminoquinolines assayed. In contrast, a large variation in the measured binding affinity was observed for the 6-position extended 2-aminoquinoline compounds tested even with small structural differences between compounds, and several compounds were obtained which bound to the Tec SH3 domain with stronger binding affinity than any other small-molecule ligand tested to date.

These results indicate that further studies of novel 6-position extended 2-aminoquinoline SH3 domain ligands is the most promising area for further investigation and optimisation of binding affinity. Addition of the phenethyl-type substituents at the 3-position of the 2-aminoquinoline results in a large reduction in the drug-like characteristics due to the increased lipophilicity and size of substituent required to access the favourable binding interaction identified in previous work. The results of this project demonstrate that so far this has not resulted in a substantial improvement in binding affinity.

While combined 3-,6-position extended 2-aminoquinoline ligands might be expected to access both favourable binding interactions, the large size of these compounds and the lipophilic substituent that appears to be required at the 3-position means that this type of compound is unlikely to have suitable water solubility for assays with the Tec SH3 domain. It also seems unlikely that the 3-position substituent would significantly contribute to improving the binding affinity when weighed against the undesirable costs of increased size and hydrophobicity of the substituent, and a significantly longer and more complicated synthesis would be required to make these larger quinoline compounds.

The 6-position extended 2-aminoquinoline ligands made in this work were determined to have a substantial improvement in binding affinity, with results indicating that further improvements are likely, and this was achieved even while improving the water solubility of the ligands. From this, it is apparent that further exploration in that area is more likely to yield the strongest binding ligands with improved drug-like characteristics.

5.4 Proposed future work

5.4.1 Investigation of tetrahydropyridine formation and stability

The production of a tetrahydropyridine side-product under Horner-Emmons conditions was among the more unexpected synthetic results of the project. Tetrahydropyridines are notoriously difficult to selectively synthesise, and no previous synthesis of these types of compounds using

similar conditions has been reported previously. The mechanism for this was not explored as part of this project, although it was experimentally verified that the tetrahydropyridine and benzylidenepiperidine isomers could interconvert under basic conditions (Figure 91).

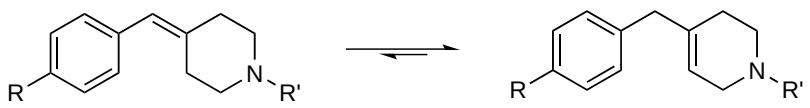


Figure 91: Isomerisation of benzylidenepiperidine and tetrahydropyridine compounds.

In some cases, depending upon the benzyl substituent, the tetrahydropyridine product was the major product. As these unsaturated heterocyclic structures are of interest in organic synthesis and drug design, it would be desirable to investigate the mechanism of formation of this product under the basic reaction conditions, and investigate the factors determining which of the isomers is the major product. If reaction or isolation conditions could be determined which exclusively produce the tetrahydropyridine product, this would be a convenient and much milder synthesis of these types of compounds than methods reported in the literature.

Extended 2-aminoquinoline compounds with a 6-position tetrahydropyridine substituent (Figure 92) are desirable future targets as they are structurally similar to the piperidine-extended compounds which have proven to be the most effective ligands for the Tec SH3 domain to date. It was found that while 2-chloroquinolines with a 6-position tetrahydropyridine substituent could be readily synthesised using the non-selective methods, the corresponding 2-aminoquinolines could not be successfully isolated. If an alternate and reliable synthesis were developed it is possible the tetrahydropyridine-extended 2-aminoquinoline ligands would be more viable targets, and the effect of this structural change upon the strength of the binding interaction with the Tec SH3 domain could be investigated.

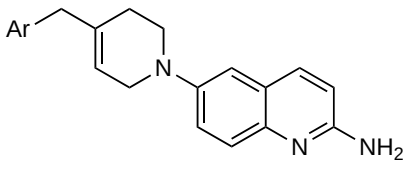


Figure 92: Target tetrahydropyridine-extended 2-aminoquinoline compounds.

5.4.2 Binding assays of most effective ligands

The SPR assay method was effectively utilised as a high-throughput screening method to identify the most promising Tec SH3 domain ligands, but further information is required

to investigate the binding interaction. The NMR chemical shift perturbation experiments could be used to investigate which SH3 domain residues are affected upon binding of the 2-aminoquinoline ligands. In particular, the shift of surface residue signals including the tryptophan W215 would indicate whether these higher affinity ligands have a similar binding model and binding site to the lead compounds.

For any ligands which bind in fast exchange with the protein-ligand complex, the K_d can also be determined via this method and used as a comparison to the SPR method. As none of the previously studied compounds were sufficiently stable or had strong enough affinity for the protein target to be assayed using the SPR method, there are currently no 2-aminoquinoline derivatives which have been assayed using both SPR and NMR assay methods. A direct comparison between the two methods would be useful, and could confirm whether the SPR method is in fact an effective high-throughput method for these screening studies, and whether the affinity results are consistent across the two methods.

It is plausible, however, that for some of the 2-aminoquinoline ligands the protein and protein-ligand complex are in intermediate exchange on the NMR timescale, in which case an affinity analysis and determination of the K_d value is not possible. If this is the case, the affected residues will still give some highly valuable indication of the binding site and possibly some insight into the binding model.

The piperidine-extended 2-aminoquinoline derivatives with a biaryl group are perhaps the most interesting compounds which should be assayed using the NMR method. Biphenyl compounds reported previously exhibited atypical binding behaviour when assayed with the Tec SH3 domain, and it was postulated that this was due to alternating binding to two favourable interactions which could not be accessed simultaneously by those ligands. With the different structures of the biaryl-extended piperidine compounds investigated for binding using the SPR method, it is possible that the issues with the multiple binding sites may have been resolved and the NMR chemical shift perturbation assays may indicate that both interactions are accessed simultaneously. If this is not the case, then design of alternate biaryl-type structures which optimally bind to the SH3 domain needs further investigation.

5.4.3 Further development of strong binding Tec SH3 domain ligands

While significantly improvements in binding affinity were obtained with these extended 2-aminoquinoline compounds, a stronger binding ligand would enable determination of the 3D structure of the protein-ligand complex by NMR spectroscopy or X-ray crystallography. With the accurate information on the ligand binding site and orientation, the 3D structure would enable any additional binding opportunities to be optimally accessed, and potentially enable more efficient and informed design if SH3 domain ligands for other potential targets.

The SPR assay results gave promising indications that stronger binding ligands could be achieved. The 6-position extended 2-aminoquinolines are the strongest binding ligands for the Tec SH3 domain found to date, and many large and structurally diverse substituents were tolerated, and therefore further structural changes can reasonably be expected to bind favourably with the Tec SH3 domain. A 4-piperidine extension at the 6-position of the quinoline ring with an electron deficient benzyl-type substituent was the most favoured scaffold in the strongest binding ligands, particularly

In cases where an aromatic ring accessed an additional favourable binding interaction, it was always found that replacing a benzene ring with a heteroaromatic ring could improve the strength of the binding interaction. This replacement is also favourable from a drug design perspective as heteroaromatic rings, especially pyrimidines, reduce the largely hydrophobic character of the ligands. From this, it is proposed that the strongly binding ligands which contained a benzene ring (**101** and **116c**) would be even more effective ligands if a pyridine or pyrimidine ring was instead utilised (Figure 93).

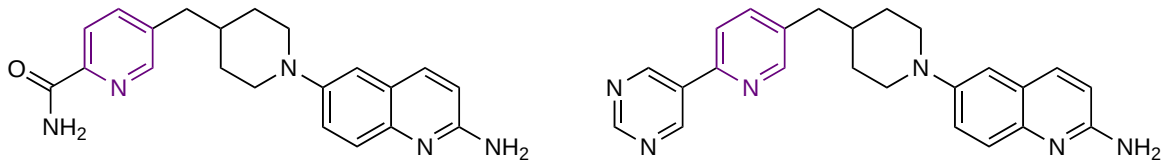


Figure 93: Proposed pyridine analogues of strongest binding ligands to date (**101** and **116c**), predicted to have improved binding affinity and improved aqueous solubility.

A broad range of substituted benzylpiperidines were investigated as 6-position 2-aminoquinoline extensions, and the most favourable substituents were all groups which were comparatively hydrophilic and electron withdrawing by resonance. These substituents were prepared as *para*-substituted derivatives due to the complications in the synthetic pathway, but alternate structures should also be investigated given the observed favourable impact upon binding. A wider array of functionalisations could be considered using simple substituents such as amidines, ketones, or charged groups (Figure 94). Alternatively, larger heteroaromatic systems such as quinoline or quinazoline rings could be investigated as alternate electron-poor structures.

A wide variety of substituent shapes and sizes were tolerated upon binding to the Tec SH3 domain, and larger substituents may also be tolerated. Addition of a biaryl group improved the strength of the binding interaction, but when compared to previous studies of biphenyl extended ligands it appears plausible that the optimal position has not been achieved. The binding affinity of *ortho*-biaryls (such as **114a**, **116a**) was not as strong, and therefore further spacing between the 2-aminoquinoline ring and the biaryl group may be more likely to reach the optimal binding position. As mentioned above, NMR chemical shift perturbation assays can be used to explore the residues involved in the binding interaction, and comparison of the

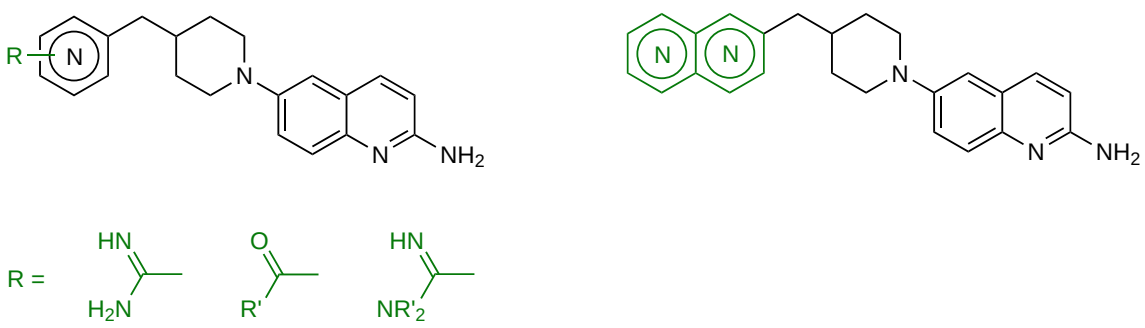


Figure 94: 6-Position extended 2-aminoquinoline derivatives with alternate electron-withdrawing functional groups.

behaviour with the results for previously reported biphenyl ligands would indicate whether the binding issues have been resolved.

One possibility is that the biaryl group is too rigid or planar to bind optimally to the SH3 domain surface, or that the biaryl group has a separate binding site on the Tec SH3 domain binding surface. In this case, alternate structures which have the second of the aromatic rings further away from the 2-aminoquinoline core structure could be favoured instead. As electron-withdrawing by resonance substituents on the 6-position benzylpiperidine extended ligands were found to be favourable for binding affinity, the use of groups such as ketones or amides as bridging groups between heteroaromatic rings may be an optimal design strategy (Figure 95).

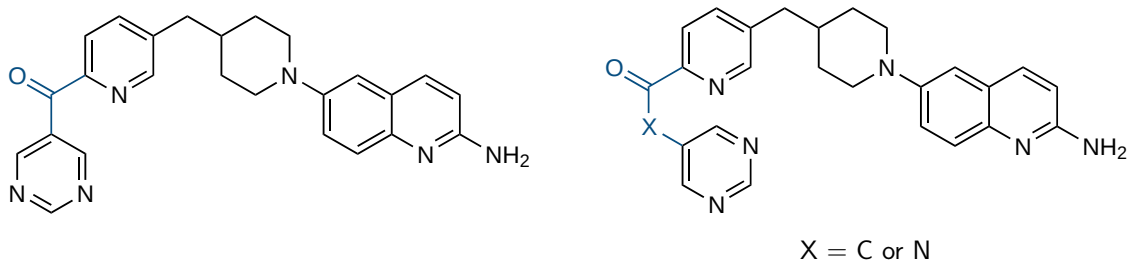


Figure 95: Alternate structures of 6-position extended 2-aminoquinoline derivatives with bridging of heteroaromatic rings.

Interestingly, none of the small structural changes which led to the strongest binding ligands in this work are mutually incompatible. More complex exotic structures can be envisaged which combine biaryl groups, electron-withdrawing functional groups, and heteroaromatic rings into a compound which has even more favourable drug-like characteristics (for example, Figure 96).

Due to the low millimolar-range K_d values obtained in this work, it is expected that such complex structures are likely not required to obtain a strongly bound protein-ligand complex.

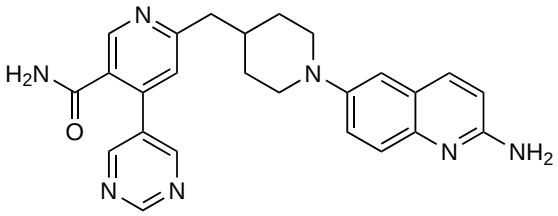


Figure 96: Structure of complex potential ligand, combining favourable structures identified from SPR assays of 2-aminoquinoline derivatives with the Tec SH3 domain.

Even if not required for affinity, the results of this work indicate that there is substantial scope to modify the 6-position 2-aminoquinoline structure while still being readily accommodated by the Tec SH3 domain, which may be useful to further improve the drug-like characteristics of the ligands or better achieve more targeted selectivity for one SH3 domain once proximate residues in the binding site are identified.

6 Experimental

6.1 General Procedures

Commercially available reagents and reagent grade solvents were used without further purification unless otherwise indicated. Anhydrous THF was collected from a PureSolv Micro Solvent Purification System and stored over 4Å molecular sieves under nitrogen gas. Anhydrous DMF was stored on 4Å molecular sieves. Other required reagents and solvents were purified according to accepted methods.[99]

Reactions were monitored where possible by TLC on MERCK aluminium-backed silica gel 60 F254 plates and visualized under UV light at 254 nm before staining with permanganate stain and heating. Flash column chromatography was performed using Davisil (40-63 micron) grade silica gel. All ^{1}H NMR (499.818 MHz), ^{13}C NMR (125.692 MHz) and ^{19}F NMR (470.256 MHz) spectra were obtained using an Agilent DD2 NMR spectrometer at 26°C unless otherwise indicated. NMR spectra of samples were collected as solutions in $CDCl_3$, D_2O, d_6-DMSO or d_6-acetone. Chemical shifts for samples in D_2O, d_6-DMSO or d_6-acetone were calibrated against the residual solvent signal,[100] and chemical shifts of samples dissolved in $CDCl_3$ were reported relative to tetramethylsilane (0.03% v/v) as an internal reference. The following abbreviations for hydrogen multiplicities were used: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; br, broad; m, multiplet. ‡ Indicates an unresolved *J* coupling constant. Chemical shifts were measured directly from the collected spectra except where non-first order analysis was used, in which case the multiplicity of the strongly-coupled spin system is denoted using Pople notation as '*AB*' or '*ABX*' and the reported chemical shifts and *J* values were determined using established analytical methods.[101] For 6-membered saturated heterocycles which adopt a chair-like conformation, inequivalent axial and equatorial hydrogen atoms are distinguished with subscripts 'ax' and 'eq' respectively (e.g. H_{ax} and H_{eq}).

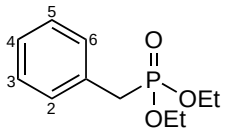
The ^{1}H and ^{13}C NMR signals of previously unreported compounds were assigned with the assistance of COSY, ROESY, HSQC and HMBC 2D NMR experiments where required. HRMS (ESI, positive ion mode) experiments of samples dissolved in acetonitrile were run using an Agilent Series 6230 TOF LC/MS spectrometer. Indicative melting points for solids were obtained using a DigiMelt MPA161 apparatus.

Aside from novel compounds, all spectroscopic data obtained in this project was compared to literature and a notation indicates that the results are consistent with that reported previously. In some instances only ^{1}H NMR data had been reported in the literature and this data was inconsistent with that obtained in this project, and these are also noted.

6.2 2-Aminoquinolines with a 6-position benzylpiperidine substituent

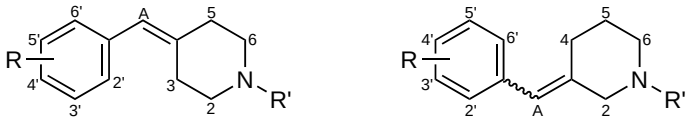
6.2.1 Synthesis of 4-benzylpiperidine derivatives

General Method 1: Synthesis of benzylphosphonate derivatives



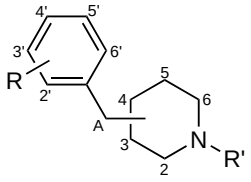
A mixture of the benzyl halide derivative (1 eq) and triethylphosphite (3 eq) was heated at reflux for 18 hr. The excess triethylphosphite was removed by short-path distillation under reduced pressure to give the phosphonate which was used without further purification.

General Method 2: Synthesis of *N*-protected benzylidenepiperidine derivatives via Horner-Emmons reaction



A solution of benzylphosphonate **36** (2 eq) in dry THF was added to a suspension of sodium hydride (60% in mineral oil, 4 eq) in THF under an atmosphere of nitrogen. The mixture was stirred for 30 min and a solution of *N*-protected piperidone (1 eq) in THF was added dropwise. The mixture was stirred at 50°C for the specified time then quenched with brine solution and extracted with ethyl acetate (3 x 40 mL). The organic extracts were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel with the specified eluant.

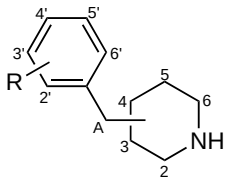
General Method 3: Synthesis of benzylpiperidine derivatives via hydrogenation reaction



The benzylidenepiperidine derivative was dissolved in methanol and stirred for the specified time under an atmosphere of hydrogen with a catalytic amount of 5% palladium on carbon (Pd-C) catalyst. The mixture was filtered through Celite® washing with methanol, and solvent

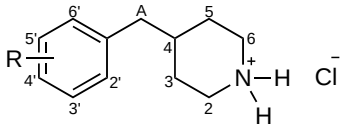
was removed under reduced pressure. The residue was purified by column chromatography on silica gel using the specified eluant where necessary, or used without further purification.

General Method 4: Synthesis of benzylpiperidine derivatives via Boc-deprotection with trifluoroacetic acid



The Boc-protected piperidine derivative (1 eq) was dissolved in dichloromethane (4.0 mL/100 mg reagent). Trifluoroacetic acid (1.0 mL/100 mg reagent) was added dropwise and the mixture was stirred at room temperature for 1 hr. The mixture was quenched with saturated aqueous sodium bicarbonate solution (30 mL) and extracted with dichloromethane (3 x 40 mL). The organic extracts were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was resuspended in dichloromethane (10 mL) and concentrated to dryness by evaporation under reduced pressure, and this was repeated until there was no trace of residual trifluoroacetic acid by ^{19}F NMR spectroscopy. The product was used without further purification.

General Method 5: Multi-step synthesis of benzylpiperidine hydrochloride derivatives via Horner-Emmons reaction

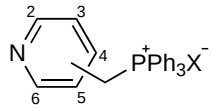


A solution of benzylphosphonate **36** (2 eq) in dry THF was added to a suspension of sodium hydride (60% in mineral oil, 4 eq) in THF under an atmosphere of nitrogen. The mixture was stirred for 30 min and a solution of Boc-protected piperidone (1 eq) in THF was added dropwise. The mixture was stirred at 50°C until complete then quenched with brine solution and extracted with ethyl acetate. The solvent was removed under reduced pressure then the residue was dissolved in methanol and stirred for 2 hr under an atmosphere of hydrogen with a catalytic amount of 5% palladium on carbon (Pd-C). The mixture was filtered through Celite®, washed with methanol, then the solvent was removed under reduced pressure. The crude residue was resuspended in ether and filtered to remove insoluble impurities. Hydrogen chloride solution (1M in diethyl ether or 4M in 1,4-dioxane) was added then the mixture was stirred at room temperature overnight. The precipitate was collected by vacuum filtration and washed with diethyl ether.

General Method 6: Conversion of benzylpiperidine hydrochloride derivatives to free amines

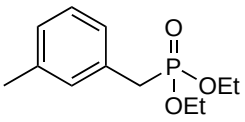
The benzylpiperidine hydrochloride derivative was suspended in dichloromethane and stirred at room temperature. Saturated aqueous sodium bicarbonate solution (20 mL) was added dropwise and the mixture was stirred for 10 minutes. The solvent was removed by evaporation under reduced pressure to give a dry residue which was extracted with dichloromethane (3 x 30 mL). The organic extracts were dried over $MgSO_4$, filtered, and solvent was removed under reduced pressure. The residue was used without further purification.

General Method 7: Synthesis of pyridinyl Wittig reagents



The chloromethylpyridine hydrochloride or bromomethylpyridine hydrobromide derivative (1.0 eq) was suspended in toluene (10 mL/1 g reagent). Saturated aqueous sodium bicarbonate solution (10 mL/1 g reagent) was slowly added and the mixture was left until visible signs of reaction ceased. The layers were separated and the aqueous layer was further extracted with toluene (2 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. Triphenylphosphine (1.5 eq) was added to the filtrate and the mixture was heated at reflux for the specified time. The reaction mixture was cooled to 0°C and the precipitate was collected by vacuum filtration, washing with toluene, to give the Wittig reagent which was used without further purification.

Diethyl 3-methylbenzylphosphonate (36c)

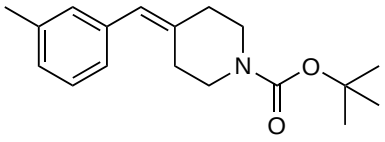


Using General Method 1, 3-methylbenzyl chloride (3.06 g, 22 mmol) and triethylphosphite (11.2 mL, 65 mmol) was were reacted for 18 hr. Removal of the excess reagent via distillation gave **36c** as a clear oil (5.61 g, >100%*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 [6H, t, ^3J = 7.1 Hz, 2 x CH_3], 2.33 [3H, s, CH_3], 3.11 [2H, d, $^2J_{H,P}$ = 21.5 Hz, PCH_2], 3.96-4.06 [4H, m, 2 x OCH_2], 7.02-7.14 [3H, m, H(2) + H(4) + H(6)], 7.19 [1H, t, $^3J_{4,5} = {}^3J_{5,6}$ = 7.6 Hz, H(5)].

This data is consistent with that reported in literature.[66]

*contains residual triethylphosphite, <5% by ^{1}H NMR analysis.

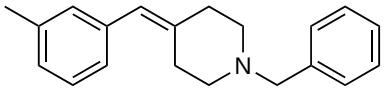
tert-Butyl 4-(3-methylbenzylidene)piperidine-1-carboxylate (45c)



Synthesis method a. Using General Method 2, **36c** (0.50 g, 2.1 mmol), *N*-Boc-4-piperidone (250 mg, 1.3 mmol), and sodium hydride (60% dispersion in paraffin oil, 300 mg, 7.5 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45c** as a colourless oil (312 mg, 87%). $R_f = 0.27$ (1:19 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{25}NO_2 - C(CH_3)_3$: 232.1338; found 232.1332. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.27-2.37 [5H, m, H(5) + CH_3], 2.43-2.51 [2H, m, H(3)], 3.33-3.44 [2H, m, H(2)], 3.45-3.55 [2H, m, H(6)], 6.33 [1H, s, H(A)], 6.97-7.05 [3H, m, H(2') + H(4') + H(6')], 7.20 [1H, t, $^3J_{4',5'} = {}^3J_{5',6'} = 7.5$ Hz, H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.57 [CH_3], 28.60 [^{t}Bu], 29.37 [C(3)], 36.35 [C(5)], 45.24 [br, C(2) + C(6)], 79.65 [^{t}Bu], 124.71 [C(A)], 126.06 [C(6')], 127.19 [C(4')], 128.18 [C(5')], 129.72 [C(2')], 137.50 [C(4)], 137.84 [C(1')], 138.33 [C(3')], 154.90 [C=O].

Synthesis method b. *N*-Boc-4-piperidone (100 mg, 0.05 mmol) and **36c** (146 mg, 0.60 mmol) were combined in ethanol (4 mL) with water (1 drop). Potassium hydroxide pellets (0.14 g, 2.5 mmol) were added over 10 minutes. The mixture was stirred at room temperature for 30 min then 70°C for 2 hr, before cooling to 60°C and adding ice water (10 mL). The mixture was extracted with ethyl acetate (3 x 30 mL) to give recovered starting materials.

1-Benzyl-4-(3-methylbenzylidene)piperidine (47c)

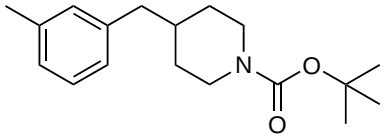


Using General Method 2, **36c** (0.38 g, 1.6 mmol), *N*-Bn-4-piperidone **46** (0.20 g, 1.1 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.13 g, 3.2 mmol) were reacted in THF (5 mL) for 4 hr. The crude product was purified by column chromatography on silica gel eluting with 3:7 ethyl acetate/hexane to give **47c** as a colourless oil (176 mg, 60%). $R_f = 0.24$ (1:4 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{20}H_{23}N$: 278.1909; found 278.1904. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.35 [2H, s, CH_3], 2.37-2.47 [4H, m, H(3) + H(5)], 2.51-2.58 [4H, m, H(2) + H(6)], 3.55 [2H, s, CH_2], 6.26 [1H, s, H(A)], 6.99-7.05 [3H, m, H(2') + H(4') + H(6')], 7.17-7.24 [1H, m, H(5')], 7.30-7.38 [5H, m, Ph]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.59 [CH_3], 29.34 [C(3)], 36.65 [C(5)], 54.59 [*C(2) or C(6)], 55.24 [*C(2) or C(6)], 63.16 [CH_2], 123.31 [C(A)], 126.13 [C(6')], 126.92 [C(4')], 127.10 [C(4'')], 128.10

[C(5')], 128.31 [C(3'') + C(5'')], 129.29 [C(2'') + C(6'')], 129.78 [C(2')], 137.73 [C(1')], 137.95[C(1'')], 138.63 [C(4)], 139.70 [C(3')].

*Interpretation of spectra and 2D NMR correlations could not achieve unambiguous assignment of all NMR signals due to overlapped signals in the ^{1}H NMR spectrum.

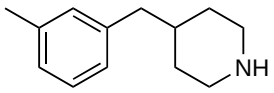
***tert*-Butyl 4-(3-methylbenzyl)piperidine-1-carboxylate (48c)**



Using General Method 3, **45c** (138 mg, 0.48 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up and column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane gave **48c** as a colourless oil (137 mg, 99%). $R_f = 0.44$ (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{27}NO_2$: 290.2120; found 290.2121*. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 12.0$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 3.3$ Hz, $H(3_{ax}) + H(5_{ax})$], 1.45 [9H, s, ^{t}Bu], 1.56-1.70 [3H, m, $H(3_{eq}) + H(4_{ax}) + H(5_{eq})$], 2.33 [3H, s, CH_3], 2.49 [2H, d, $^{3}J_{4ax,A} = 6.9$ Hz, H(A)], 2.63 [2H, br t‡, $^{2}J_{(2/6)ax,(2/6)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = 12.0$ Hz, $H(2_{ax}) + H(6_{ax})$], 3.82-4.29 [2H, m, $H(2_{eq}) + H(6_{eq})$], 6.90-6.97 [2H, m, H(2') + H(6')], 7.00 [1H, br d‡, $^{3}J_{4',5'} = 7.5$ Hz, H(4')], 7.16 [1H, t, $^{3}J_{4',5'} = {}^{3}J_{5',6'} = 7.5$ Hz, H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.53 [CH_3], 28.61 [^{t}Bu], 32.17 [br, C(3) + C(5)], 38.30 [C(4)], 43.22 [C(A)], 44.05 [br, C(2) + C(6)], 79.31 [^{t}Bu], 126.26 [C(6')], 126.78 [C(4')], 128.22 [C(5')], 130.04 [C(2')], 137.88 [C(3')], 140.31 [C(1')], 155.00 [C=O].

*Only trace of parent ion mass peak observed. Predominant mass peak corresponds to fragment: HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{27}NO_2 - C(CH_3)_3$: 234.1494; found 234.1491.

4-(3-Methylbenzyl)piperidine (31c)



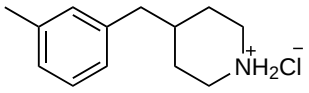
Synthesis method a. Using General Method 4, **48c** (89 mg, 0.31 mmol) and trifluoroacetic acid (1 mL) were reacted in dichloromethane (4 mL) to give **31c** as a yellow oil (51 mg, 88%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{13}H_{19}N$: 190.1596; found 190.1587. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 12.7$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 3.9$ Hz, $H(3_{ax}) + H(5_{ax})$], 1.65-1.81 [3H, m, $H(3_{eq}) + H(4_{ax}) + H(5_{eq})$], 2.33 [3H, s, CH_3], 2.53 [2H, d, $^{3}J_{A,4ax} = 7.0$ Hz, H(A)], 2.71 [2H, td, $^{2}J_{(2/6)ax,(2/6)eq} =$

$^{3}J_{(2/6)ax,(3/5)ax}$ = 12.7 Hz, $^{3}J_{(2/6)ax,(3/5)eq}$ = 2.7 Hz, H(2_{ax}) + H(6_{ax})], 3.00 [1H, br s, NH], 3.26 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq}$ = 12.7 Hz, H(2_{eq}) + H(6_{eq})], 6.90-6.97 [2H, m, H(2') + H(6')], 7.02 [1H, br d‡, $^{3}J_{4',5'}$ = 7.6 Hz, H(4')], 7.17 [1H, t, $^{3}J_{4',5'}$ = $^{3}J_{5',6'}$ = 7.6 Hz, H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.50 [CH_3], 31.02 [C(3) + C(5)], 37.34 [C(4)], 43.11 [C(A)], 45.33 [C(2) + C(6)], 126.21 [C(6')], 126.94 [C(4')], 128.30 [C(5')], 129.98 [C(2')], 138.00 [C(3')], 139.76 [C(1')].

This data is consistent with that reported in literature.[58]

Synthesis method b. Using General Method 6, **49c** (87 mg, 0.39 mmol) was treated with saturated aqueous sodium bicarbonate solution (10 mL) in dichloromethane (10 mL) to give **31c** as a yellow oil (50 mg, 69%). Data as above.

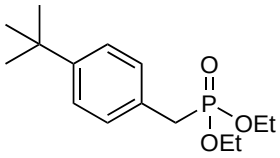
4-(3-Methylbenzyl)piperidine hydrochloride (49c)



Synthesis method a. Using General Method 5, **36c** (0.50 g, 2.1 mmol), *N*-Boc-4-piperidone (0.21 g, 1.1 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.34 g, 8.5 mmol) were reacted for 18 hr in THF (5 mL), then with Pd-C in methanol (20 mL) for 2 hr followed by hydrogen chloride solution (1M in diethyl ether, 1.5 mL) in diethyl ether (3 mL), to give **49c** as a brown solid (0.14 g, 60%). ^{1}H NMR (500 MHz, D_2O): δ 1.32 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq}$ = $^{3}J_{(2/6)ax,(3/5)ax}$ = $^{3}J_{(3/5)ax,4ax}$ = 12.8 Hz, $^{3}J_{(2/6)eq,(3/5)ax}$ = 3.9 Hz, H(3_{ax}) + H(5_{ax})], 1.70-1.85 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.21 [3H, s, CH_3], 2.49 [2H, d, $^{3}J_{4ax,A}$ = 6.9 Hz, H(A)], 2.82 [2H, br t‡, $^{2}J_{(2/6)ax,(2/6)eq}$ = $^{3}J_{(2/6)ax,(3/5)ax}$ = 12.8 Hz, H(2_{ax}) + H(6_{ax})], 3.29 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq}$ = 12.8 Hz, H(2_{eq}) + H(6_{eq})], 6.97 [1H, d, $^{3}J_{4',5'}$ = 7.7 Hz, H(4')], 6.99-7.06 [2H, m, H(2') + H(6')], 7.17 [1H, t, $^{3}J_{4',5'}$ = $^{3}J_{5',6'}$ = 7.7 Hz, H(5')]. ^{13}C NMR (126 MHz, D_2O): δ 22.94 [CH_3], 30.74 [C(3) + C(5)], 37.64 [C(4)], 43.90 [C(A)], 46.66 [C(2) + C(6)], 128.86 [C(6')], 129.46 [C(4')], 131.13 [C(5')], 132.50 [C(2')], 141.25 [C(3')], 142.68 [C(1')].

Synthesis method b. Using General Method 5, **36c** (0.50 g, 2.1 mmol), *N*-Boc-4-piperidone (0.21 g, 1.1 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.34 g, 8.5 mmol) were reacted for 18 hr in THF (5 mL), then with Pd-C in methanol (20 mL) for 2 hr followed by hydrogen chloride solution (4M in 1,4-dioxane, 2 mL), to give **49c** as a brown solid (89 mg, 37%). Data as above.

Diethyl 4-*tert*-butylbenzylphosphonate (36a)

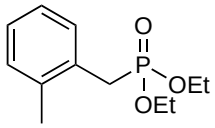


Using General Method 1, 4-(*tert*-butyl)benzyl bromide (2.50 g, 11 mmol) was reacted with triethylphosphite (5.6 mL, 33 mmol) to give **36a** as a clear oil (3.25 g, >100%*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 [6H, t, ^{3}J = 7.1 Hz, 2 x CH_3], 1.30 [9H, s, ^{t}Bu], 3.12 [2H, d, $^{2}J_{H,P}$ = 21.4 Hz, PCH_2], 3.96-4.07 [4H, m, 2 x OCH_2], 7.20-7.26 [2H, m, H(2) + H(6)], 7.30-7.35 [2H, m, H(3) + H(5)].

This data is consistent with that reported in literature.[102]

*contains residual triethylphosphite, <5% by ^{1}H NMR analysis.

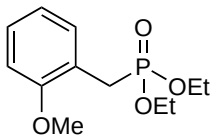
Diethyl 2-methylbenzylphosphonate (36b)



Using General Method 1, 2-methylbenzyl bromide (3.0 g, 16 mmol) was reacted with triethylphosphite (8.3 mL, 49 mmol) to give **36b** as a clear oil (3.92 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 [6H, t, ^{3}J = 7.1 Hz, 2 x CH_3], 2.39 [3H, s, CH_3], 3.17 [2H, d, $^{2}J_{H,P}$ = 22.0 Hz, PCH_2], 3.91-4.09 [4H, m, 2 x OCH_2], 7.11-7.20 [3H, m, H(4) + H(5) + H(6)], 7.23-7.31 [1H, m, H(3)].

This data is consistent with that reported in literature.[66]

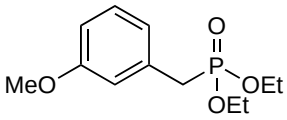
Diethyl 2-methoxybenzylphosphonate (36e)



Using General Method 1, 2-methoxybenzyl chloride (0.36 g, 2.3 mmol) was reacted with triethylphosphite (1.2 mL, 7.0 mmol) to give **36e** as a pale yellow oil (0.52 g, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 [6H, t, ^{3}J = 7.2 Hz, 2 x CH_3], 3.25 [2H, d, $^{2}J_{H,P}$ = 21.7 Hz, PCH_2], 3.84 [3H, s, OCH_3], 4.02 [4H, p, ^{3}J = $^{3}J_{H,P}$ = 7.2 Hz, 2 x OCH_2], 6.86 [1H, d, $^{3}J_{3,4}$ = 7.8 Hz, H(3)], 6.91 [1H, t, $^{3}J_{4,5}$ = $^{3}J_{5,6}$ = 7.8 Hz, H(5)], 7.22 [1H, br t‡, $^{3}J_{3,4}$ = $^{3}J_{4,5}$ = 7.8 Hz, H(4)], 7.32 [1H, br d‡, $^{3}J_{5,6}$ = 7.8 Hz, H(6)].

This data is consistent with that reported in literature.[103]

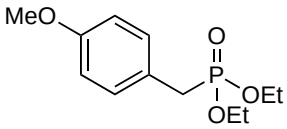
Diethyl 3-methoxybenzylphosphonate (36f)



Using General Method 1, 3-methoxybenzyl chloride (2.50 g, 16 mmol) was reacted with triethylphosphite (8.21 mL, 48 mmol) to give **36f** as a pale yellow oil (3.82 g, 93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 [6H, t, ^{3}J = 7.1 Hz, 2 x CH_3], 3.13 [2H, d, $^{2}J_{H,P}$ = 21.6 Hz, PCH_2], 3.80 [3H, s, OCH_3], 3.96-4.08 [4H, m, 2 x OCH_2], 6.79 [1H, ddt, $^{3}J_{5,6}$ = 8.1 Hz, $^{4}J_{H,P}$ = 2.4 Hz, $^{4}J_{2,6}$ = $^{4}J_{4,6}$ = 1.0 Hz, H(6)], 6.84-6.91 [2H, m, H(2) + H(4)], 7.22 [1H, t, $^{3}J_{4,5}$ = $^{3}J_{5,6}$ = 8.1 Hz, H(5)].

This data is consistent with that reported in literature.[103]

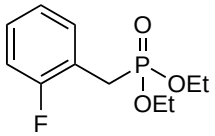
Diethyl 4-methoxybenzylphosphonate (36g)



Using General Method 1, 4-methoxybenzyl chloride (2.50 g, 16 mmol) was reacted with triethylphosphite (8.21 mL, 48 mmol) to give **36g** as a pale yellow oil (3.91 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 [6H, t, ^{3}J = 7.1 Hz, 2 x CH_3], 3.09 [2H, d, $^{2}J_{H,P}$ = 21.2 Hz, PCH_2], 3.79 [3H, s, OCH_3], 3.95-4.06 [4H, m, 2 x OCH_2], 6.82-6.88 [2H, m, H(3) + H(5)], 7.18-7.25 [2H, m, H(2) + H(6)].

This data is consistent with that reported in literature.[103]

Diethyl 2-fluorobenzylphosphonate (36h)

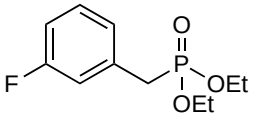


Using General Method 1, 2-fluorobenzyl chloride (3.15 g, 21.8 mmol) was reacted with triethylphosphite (11.2 mL, 65.3 mmol) to give **36h** as a yellow oil (5.21 g, 97%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 [6H, t, ^{3}J = 7.1 Hz, 2 x CH_3], 3.20 [2H, d, $^{2}J_{H,P}$ = 21.6 Hz, PCH_2], 3.99-4.10 [4H, m, 2 x OCH_2], 7.05 [1H, dd, $^{3}J_{H,F}$ = 9.5 Hz, $^{3}J_{3,4}$ = 8.7 Hz, H(3)], 7.10 [1H, t, $^{3}J_{4,5}$ = $^{3}J_{5,6}$ = 7.6 Hz, H(5)], 7.23 [1H, ddddd, $^{3}J_{3,4}$ = 8.7 Hz, $^{3}J_{4,5}$ =

7.6 Hz, $^{4}J_{H,F}$ = 5.3 Hz, $^{6}J_{H,P}$ = 2.1 Hz, $^{4}J_{4,6}$ = 2.0 Hz, H(4)], 7.38 [1H, tt, $^{3}J_{5,6}$ = $^{4}J_{H,F}$ = 7.6 Hz, $^{4}J_{4,6}$ = $^{4}J_{H,P}$ = 2.0 Hz, H(6)].

This data is consistent with that reported in literature.[66]

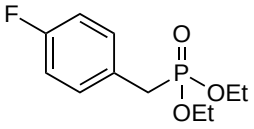
Diethyl 3-fluorobenzylphosphonate (36i)



Using General Method 1, 3-fluorobenzyl bromide (2.84 g, 15.0 mmol) was reacted with triethylphosphite (7.7 mL, 45.1 mmol) to give **36i** as a yellow oil (3.31 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 [6H, t, ^{3}J = 7.1 Hz, 2 x CH_3], 3.14 [2H, d, $^{2}J_{H,P}$ = 21.8 Hz, PCH_2], 3.98-4.10 [4H, m, 2 x OCH_2], 6.95 [1H, tt, $^{3}J_{4,5}$ = $^{3}J_{H,F}$ = 8.4 Hz, $^{4}J_{2,4}$ = $^{4}J_{4,6}$ = 2.5 Hz, H(4)], 7.03 [1H, dq, $^{3}J_{H,F}$ = 9.6 Hz, $^{4}J_{2,4}$ = $^{4}J_{4,6}$ = $^{4}J_{H,P}$ = 2.5 Hz, H(2)], 7.06-7.10 [1H, m, H(6)], 7.27 [1H, q, $^{3}J_{4,5}$ = $^{3}J_{5,6}$ = $^{4}J_{H,F}$ = 8.4 Hz, H(5)].

This data is consistent with that reported in literature.[103]

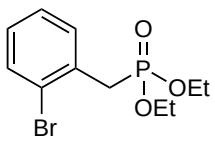
Diethyl 4-fluorobenzylphosphonate (36j)



Using General Method 1, 4-fluorobenzyl chloride (3.15 g, 21.1 mmol) was reacted with triethylphosphite (11.2 mL, 65.3 mmol) to give **36j** as a colourless oil (5.20 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 [6H, t, ^{3}J = 7.0 Hz, 2 x CH_3], 3.11 [2H, d, $^{2}J_{H,P}$ = 21.4 Hz, PCH_2], 3.97-4.06 [4H, m, 2 x OCH_2], 6.96-7.05 [2H, m, H(3) + H(5)], 7.22-7.31 [2H, m, H(2) + H(6)].

This data is consistent with that reported in literature.[104]

Diethyl 2-bromobenzylphosphonate (36k)



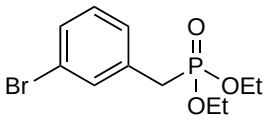
Using General Method 1, 2-bromobenzyl bromide (5.00 g, 20.0 mmol) was reacted with triethylphosphite (10.3 mL, 60.0 mmol) to give **36k** as a colourless oil (6.52 g, >100%*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 [6H, t, ^{3}J = 7.1 Hz, 2 x CH_3], 3.41 [2H, d, $^{2}J_{H,P}$ = 22.0

Hz, PCH_2], 4.01-4.09 [4H, m, 2 x OCH_2], 7.10 [1H, tt, $^3J_{3,4} = {}^3J_{4,5} = 7.8$ Hz, $^4J_{4,6} = {}^6J_{H,P} = 2.0$ Hz, H(4)], 7.27 [1H, t, $^3J_{4,5} = {}^3J_{5,6} = 7.8$ Hz, H(5)], 7.47 [1H, ddd, $^3J_{5,6} = 7.8$ Hz, $^4J_{H,P} = 2.4$ Hz, $^4J_{4,6} = 2.0$ Hz, H(6)], 7.58 [1H, d, $^3J_{3,4} = 7.8$ Hz, H(3)].

This data is consistent with that reported in literature.[66]

*contains residual triethylphosphite, <5% by ^{1}H NMR analysis.

Diethyl 3-bromobenzylphosphonate (36l)

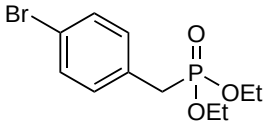


Using General Method 1, 3-bromobenzyl bromide (7.27 g, 23.3 mmol) was reacted with triethylphosphite (12.0 mL, 70.0 mmol) to give **36l** as a colourless oil (7.21 g, >100%*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 [6H, t, $^3J = 7.1$ Hz, 2 x CH_3], 3.11 [2H, d, $^2J_{H,P} = 21.7$ Hz, PCH_2], 3.98-4.08 [4H, m, 2 x OCH_2], 7.18 [1H, t, $^3J_{4,5} = {}^3J_{5,6} = 7.8$ Hz, H(5)], 7.25 [1H, br d‡, $^3J_{5,6} = 7.8$ Hz, H(6)], 7.38 [1H, br d‡, $^3J_{4,5} = 7.8$ Hz, H(4)], 7.45 [1H, br s‡, H(2)].

This data is consistent with that reported in literature.[105]

*contains residual triethylphosphite, <5% by ^{1}H NMR analysis.

Diethyl 4-bromobenzylphosphonate (36m)

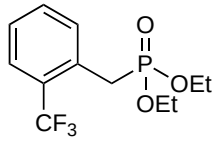


Using General Method 1, 4-bromobenzyl bromide (5.83 g, 23.3 mmol) was reacted with triethylphosphite (12.0 mL, 70.0 mmol) to give **36m** as a colourless oil (7.27 g, 100%*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 [6H, t, $^3J = 7.1$ Hz, 2 x CH_3], 3.09 [2H, d, $^2J_{H,P} = 21.7$ Hz, PCH_2], 3.96-4.09 [4H, m, 2 x OCH_2], 7.14-7.20 [2H, m, H(2) + H(6)], 7.41-7.46 [2H, m, H(3) + H(5)].

This data is consistent with that reported in literature.[66]

*contains residual triethylphosphite, <7% by ^{1}H NMR analysis.

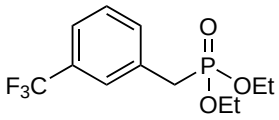
Diethyl 2-trifluoromethylbenzylphosphonate (36n)



Using General Method 1, 2-trifluoromethylbenzyl chloride (2.00 g, 10 mmol) was reacted with triethylphosphite (5.18 mL, 30 mmol) to give **36n** as a pale yellow oil (2.71 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 [6H, t, ^{3}J = 7.0 Hz, 2 x CH_3], 3.37 [2H, d, $^{2}J_{H,P}$ = 22.7 Hz, PCH_2], 3.96-4.09 [4H, m, 2 x OCH_2], 7.35 [1H, br t‡, $^{3}J_{4,5} = {}^{3}J_{5,6}$ = 7.6 Hz, H(5)], 7.51 [1H, t, $^{3}J_{3,4} = {}^{3}J_{4,5}$ = 7.6 Hz, H(4)], 7.65 [1H, d, $^{3}J_{3,4}$ = 7.6 Hz, H(3)], 7.69 [1H, br d‡, $^{3}J_{4,5}$ = 7.6 Hz, H(6)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.27 [d, $^{3}J_{C,P}$ = 6.2 Hz, CH_3], 30.19 [dq, $^{1}J_{C,P}$ = 139.7 Hz, $^{4}J_{C,F}$ = 1.9 Hz, PCH_2], 62.32 [d, $^{2}J_{C,P}$ = 7.2 Hz, OCH_2], 124.26 [qd, $^{1}J_{C,F}$ = 273.8 Hz, $^{4}J_{C,P}$ = 1.6 Hz, CF_3], 126.24 [qd, $^{3}J_{C,F}$ = 5.3 Hz, $^{4}J_{C,P}$ = 2.4 Hz, C(3)], 127.02 [br d‡, $^{3}J_{C,P}$ = 3.3 Hz, C(6)], 129.08 [qd, $^{2}J_{C,F}$ = 29.6 Hz, $^{3}J_{C,P}$ = 8.1 Hz, C(2)], 130.52 [dq, $^{2}J_{C,P}$ = 8.3 Hz, $^{3}J_{C,F}$ = 1.6 Hz, C(1)], 131.75 [br d‡, $^{4}J_{C,P}$ = 2.8 Hz, C(5)], 132.32 [br d‡, $^{5}J_{C,P}$ = 4.8 Hz, C(4)].

^{1}H NMR only reported previously,[106] but was inconsistent with data reported here.

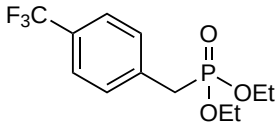
Diethyl 3-trifluoromethylbenzylphosphonate (36o)



Using General Method 1, 3-trifluoromethylbenzyl chloride (2.00 g, 10 mmol) was reacted with triethylphosphite (5.18 mL, 30 mmol) to give **36o** as a pale yellow oil (2.85 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 [6H, t, ^{3}J = 7.2 Hz, 2 x CH_3], 3.20 [2H, d, $^{2}J_{H,P}$ = 21.8 Hz, PCH_2], 4.04 [4H, p, $^{3}J_{H,P} = {}^{3}J$ = 7.2 Hz, 2 x OCH_2], 7.41-7.56 [4H, m, H(2) + H(4) + H(5) + H(6)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.32 [d, $^{3}J_{C,P}$ = 6.2 Hz, CH_3], 33.68 [d, $^{1}J_{C,P}$ = 138.8 Hz, PCH_2], 62.29 [d, $^{2}J_{C,P}$ = 6.7 Hz, OCH_2], 123.75 [p, $^{4}J_{C,F} = {}^{5}J_{C,P}$ = 3.8 Hz, C(4)], 124.01 [q, $^{1}J_{C,F}$ = 272.1 Hz, CF_3], 126.52 [dq, $^{3}J_{C,P}$ = 7.6 Hz, $^{4}J_{C,F}$ = 3.8 Hz, C(2)], 129.00 [d, $^{4}J_{C,P}$ = 2.9 Hz, C(5)], 130.84 [qd, $^{2}J_{C,F}$ = 32.4 Hz, $^{4}J_{C,P}$ = 3.2 Hz, C(3)], 132.88 [d, $^{2}J_{C,P}$ = 9.5 Hz, C(1)], 133.18 [dq, $^{3}J_{C,P}$ = 6.2 Hz, $^{5}J_{C,F}$ = 1.0 Hz, C(6)].

This data is consistent with that reported in literature.[107]

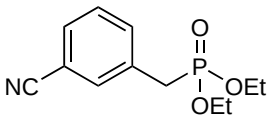
Diethyl 4-trifluoromethylbenzylphosphonate (36p)



Using General Method 1, 4-trifluoromethylbenzyl chloride (2.0 g, 10.3 mmol) was reacted with triethylphosphite (5.18 mL, 30.2 mmol) to give **36p** as a pale yellow oil (3.00 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 [6H, t, ^{3}J = 7.1 Hz, 2 x CH_3], 3.20 [2H, d, $^{2}J_{H,P}$ = 22.0 Hz, PCH_2], 4.00-4.08 [4H, m, 2 x OCH_2], 7.39-7.46 [2H, m, H(2) + H(6)], 7.54-7.60 [2H, m, H(3) + H(5)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.46 [d, $^{3}J_{C,P}$ = 5.7 Hz, CH_3], 33.86 [d, $^{1}J_{C,P}$ = 137.8 Hz, PCH_2], 62.40 [d, $^{2}J_{C,P}$ = 6.7 Hz, OCH_2], 124.25 [qd, $^{1}J_{C,F}$ = 272.0 Hz, $^{6}J_{C,P}$ = 1.7 Hz, CF_3], 125.52 [p, $^{3}J_{C,F}$ = $^{4}J_{C,P}$ = 5.6 Hz, C(3) + C(5)], 129.31 [dq, $^{2}J_{C,P}$ = 32.3 Hz, $^{5}J_{C,F}$ = 4.0 Hz, C(4)], 130.18 [d, $^{3}J_{C,P}$ = 6.7 Hz, C(2) + C(6)], 136.12 [dq, $^{2}J_{C,P}$ = 9.0 Hz, $^{5}J_{C,F}$ = 1.1 Hz, C(1)].

This data is consistent with that reported in literature.[105]

Diethyl 3-cyanobenzylphosphonate (36r)

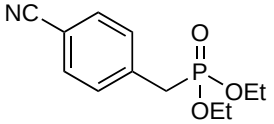


Using General Method 1, 3-(bromomethyl)benzonitrile (3.0 g, 15.3 mmol) was reacted with triethylphosphite (7.9 mL, 46.1 mmol) to give **36r** as a pale yellow oil (4.11 g, 100%*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 [6H, t, ^{3}J = 7.0 Hz, 2 x CH_3], 3.17 [2H, d, $^{2}J_{H,P}$ = 21.9 Hz, PCH_2], 4.01-4.09 [4H, m, 2 x OCH_2], 7.43 [1H, t, $^{3}J_{4,5}$ = $^{3}J_{5,6}$ = 7.8 Hz, H(5)], 7.53-7.61 [3H, m, H(2) + H(4) + H(6)].

*contains residual triethylphosphite, <7% by ^{1}H NMR analysis.

This data is consistent with that reported in literature.[108]

Diethyl 4-cyanobenzylphosphonate (36s)

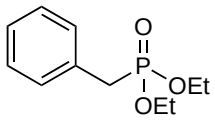


Using General Method 1, 4-(chloromethyl)benzonitrile (3.0 g, 19.8 mmol) was reacted with triethylphosphite (10.2 mL, 59.5 mmol) to give **36s** as a yellow oil (4.55 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 [6H, t, ^{3}J = 7.1 Hz, 2 x CH_3], 3.20 [2H, d, $^{2}J_{H,P}$ = 22.3 Hz,

PCH_2], 4.00-4.09 [4H, m, 2 x OCH_2], 7.38-7.46 [2H, m, H(2) + H(6)], 7.57-7.65 [2H, m, H(3) + H(5)].

This data is consistent with that reported in literature.[109]

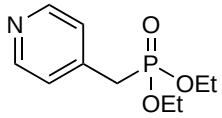
Diethyl benzylphosphonate (36x)



Using General Method 1, benzyl bromide (4.60 mL, 38.9 mmol) was reacted with triethylphosphite (20.0 mL, 117 mmol) to give **36x** as a yellow oil (8.87 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 [6H, t, ^3J = 7.1 Hz, 2 x CH_3], 3.15 [2H, d, $^2J_{H,P}$ = 21.6 Hz, PCH_2], 3.94-4.07 [4H, m, 2 x OCH_2], 7.19-7.35 [5H, m, H(2) + H(3) + H(4) + H(5) + H(6)].

This data is consistent with that reported in literature.[110]

Diethyl (pyridin-4-ylmethyl)phosphonate (50c)



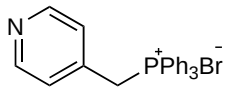
Synthesis method a. 4-(Bromomethyl)pyridine hydrobromide (0.20 g, 1.98 mmol) was suspended in toluene (15 mL). Saturated aqueous sodium bicarbonate solution (20 mL) was added, and after visible signs of reaction ceased the mixture was extracted with toluene (3 x 20 mL). The organic extracts were dried over $MgSO_4$ and filtered, then heated at reflux with triethylphosphite (1.02 mL, 5.94 mmol) for 4 hr. The resultant mixture contained a black solid which was collected by vacuum filtration. ^{1}H NMR analysis indicated there was no product **50c** or pyridine reagent present in solid or filtrate.

Synthesis method b. 4-(Bromomethyl)pyridine hydrobromide (0.20 g, 1.98 mmol) was suspended in dichloromethane (5 mL). Saturated aqueous sodium bicarbonate solution (20 mL) was added, and after visible signs of reaction ceased the mixture was extracted with dichloromethane (3 x 20 mL). The organic extracts were dried over $MgSO_4$ and filtered, then heated at reflux with triethylphosphite (1.02 mL, 5.94 mmol) for 4 hr. The remaining dichloromethane was removed by evaporation under reduced pressure. Partial removal of the triethylphosphite by short-path distillation gave a pink precipitate which was removed by gravity filtration and found by crude ^{1}H NMR analysis to contain no product. The remaining triethylphosphite was removed from the filtrate by short-path distillation to give a crude brown oil, found by ^{1}H NMR analysis to contain **50c**, which was used without further purification (86 mg, <20% yield). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{10}H_{16}NO_3P$: 230.0946; found

230.0939. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 [6H, t, ^{3}J = 7.1 Hz, 2 x CH_3], 3.13 [2H, d, $^{2}J_{H,P}$ = 22.3 Hz, PCH_2], 4.01-4.10 [4H, m, 2 x OCH_2], 7.22-7.27 [2H, m, H(2) + H(6)], 8.52-8.57 [2H, m, H(3) + H(5)].

This data is consistent with that reported in literature.[111]

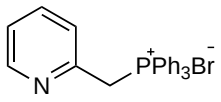
Triphenyl(pyridin-4-ylmethyl)phosphonium bromide (52c)



Using General Method 7, 4-(bromomethyl)pyridine hydrobromide (2.0 g, 7.9 mmol) in toluene was treated with saturated aqueous sodium bicarbonate solution then heated at reflux with triphenylphosphine (3.11 g, 11.9 mmol) for 3 hr to give **52c** as a pink solid (2.49 g, 75%). MP: 247-249°C. ^{1}H NMR (500 MHz, d_6-DMSO): δ 5.34 [2H, d, $^{2}J_{H,P}$ = 16.6 Hz, PCH_2], 7.00-7.07 [2H, m, H(3) + H(5)], 7.64-7.98 [15H, m, 3 x Ph], 8.42-8.49 [2H, m, H(2) + H(6)]. ^{13}C NMR (126 MHz, d_6-DMSO): δ 27.41 [d, $^{1}J_{C,P}$ = 47.2 Hz, PCH_2], 117.34 [d, $^{1}J_{C,P}$ = 86.3 Hz, C(1')], 125.99 [d, $^{3}J_{C,P}$ = 5.7 Hz, C(3) + C(5)], 130.25 [d, $^{3}J_{C,P}$ = 12.4 Hz, C(3') + C(5')], 134.00 [d, $^{2}J_{C,P}$ = 10.0 Hz, C(2') + C(6')], 135.34 [d, $^{4}J_{C,P}$ = 2.9 Hz, C(4')], 138.50 [d, $^{2}J_{C,P}$ = 8.0 Hz, C(4)], 149.42 [d, $^{4}J_{C,P}$ = 2.4 Hz, C(2) + C(6)].

^{1}H NMR only reported previously,[112] but was inconsistent with data reported here.

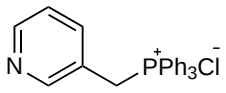
Triphenyl(pyridin-2-ylmethyl)phosphonium bromide (52a)



Using General Method 7, 2-(bromomethyl)pyridine hydrobromide (2.50 g, 9.9 mmol) in toluene was reacted with saturated aqueous sodium bicarbonate solution then heated at reflux with triphenylphosphine (4.03 g, 15.4 mmol) for 3 hr to give **52a** as a pale yellow solid (3.67 g, 85%). MP: 261-262°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.63 [2H, d, $^{2}J_{H,P}$ = 14.4 Hz, PCH_2], 7.09-7.19 [1H, m, H(4)], 7.56 [1H, t, $^{3}J_{4,5}$ = $^{3}J_{5,6}$ = 7.7 Hz, H(5)], 7.58-7.69 [6H, m, H(3') + H(5')], 7.75 [3H, t, $^{3}J_{3',4'}$ = $^{3}J_{4',5'}$ = 7.8 Hz, H(4')], 7.78-7.86 [6H, m, H(2') + H(6')], 7.88 [1H, d, $^{3}J_{5,6}$ = 7.7 Hz, H(6)], 8.25 [1H, d, $^{3}J_{4,5}$ = 4.7 Hz, H(3)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.95 [d, $^{1}J_{C,P}$ = 52.0 Hz, PCH_2], 118.76 [d, $^{1}J_{C,P}$ = 87.3 Hz, C(1')], 123.01 [d, $^{5}J_{C,P}$ = 1.9 Hz, C(5)], 126.98 [d, $^{3}J_{C,P}$ = 7.6 Hz, C(3)], 129.98 [d, $^{3}J_{C,P}$ = 12.9 Hz, C(3') + C(5')], 134.21 [d, $^{2}J_{C,P}$ = 10.0 Hz, C(2') + C(6')], 134.72 [d, $^{4}J_{C,P}$ = 2.9 Hz, C(4')], 137.42 [br‡, C(4)], 148.62 [br‡, C(6)], 149.61 [d, $^{2}J_{C,P}$ = 8.6 Hz, C(2)].

^{1}H NMR only reported previously,[113] but was inconsistent with data reported here.

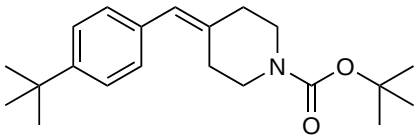
Triphenyl(pyridin-3-ylmethyl)phosphoniumchloride (52b)



Using General Method 7, 3-(chloromethyl)pyridine hydrochloride (1.96 g, 11.9 mmol) in toluene (20 mL) was treated with saturated aqueous sodium bicarbonate solution then heated at reflux with triphenylphosphine (4.71 g, 18.0 mmol) for 3 hr to give **52b** as a pink solid (1.37 g, 34%). MP: >260°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 [2H, d, $^{2}J_{H,P} = 14.9$ Hz, PCH_2], 7.09 [1H, dd, $^{3}J_{4,5} = 7.9$ Hz, $^{3}J_{5,6} = 4.8$ Hz, H(5)], 7.58-7.67 [6H, m, Ph], 7.72-7.79 [3H, m, Ph], 7.79-7.88 [6H, m, Ph], 7.91-7.96 [1H, m, H(4)], 8.08-8.12 [1H, m, H(2)], 8.40-8.44 [1H, m, H(6)]. ^{13}C NMR (126 MHz, d_6-DMSO): δ 25.47 [d, $^{1}J_{C,P} = 47.7$ Hz, PCH_2], 117.44 [d, $^{1}J_{C,P} = 85.8$ Hz, C(1')], 123.73 [d, $^{4}J_{C,P} = 2.9$ Hz, C(5)], 124.59 [d, $^{2}J_{C,P} = 8.6$ Hz,C(3)], 130.25 [d, $^{3}J_{C,P} = 12.4$ Hz, C(3') + C(5')], 134.04 [d, $^{2}J_{C,P} = 10.0$ Hz, C(2') + C(6')], 135.27 [d, $^{4}J_{C,P} = 3.3$ Hz,C(4')], 138.23 [d, $^{3}J_{C,P} = 5.3$ Hz, C(4)], 149.36 [d, $^{5}J_{C,P} = 3.8$ Hz, C(6)], 151.20 [d, $^{3}J_{C,P} = 6.2$ Hz, C(2)].

This data is consistent with that reported in literature.[114]

***tert*-Butyl 4-(4-*tert*-butylbenzylidene)piperidine-1-carboxylate (45a)**

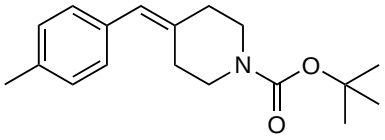


Synthesis method a. Using General Method 2, **36a** (0.71 g, 2.5 mmol), *N*-Boc-4-piperidone (0.25 g, 1.3 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.40 g, 10.0 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45a** as a colourless oil (162 mg, 39%). $R_f = 0.39$ (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{31}NO_2 - C(CH_3)_3$: 274.1807; found 274.1795. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 [9H, s, ^{t}Bu], 1.48 [9H, s, ^{t}Bu], 2.27-2.38 [2H, m, H(5)], 2.43-2.54 [2H, m, H(3)], 3.33-3.44 [2H, m, H(2)], 3.46-3.55 [2H, m, H(6)], 6.32 [1H, s, H(A)], 7.11-7.16 [2H, m, H(3') + H(5')], 7.31-7.38 [2H, m, H(2') + H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.63 [^{t}Bu], 29.22 [^{t}Bu], 29.38 [C(3)], 31.49 [^{t}Bu], 34.64 [C(5)], 36.35 [br, C(2)], 44.59 [br, C(6)], 79.66 [^{t}Bu], 124.45 [C(A)], 125.23 [C(3') + C(5')], 128.73 [C(2') + C(6')], 134.70 [C(1')], 138.00 [C(4)], 149.38 [C(4')], 154.94 [C=O].

Synthesis method b. *N*-Boc-4-piperidone (200 mg, 1.0 mmol) and **36a** (0.36 g, 1.24 mmol) were combined in ethanol (4 mL) with water (1 drop). Potassium hydroxide pellets (0.28 g, 5.0 mmol) were added over 10 minutes. The mixture was stirred at room temperature for 30

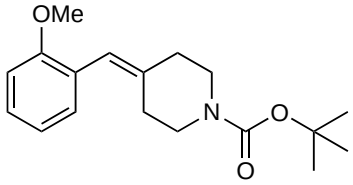
min then 70°C for 2 hr, before cooling to 60°C and adding ice water (10 mL). The mixture was extracted with ethyl acetate (3 x 30 mL) to give recovered starting materials.

tert-Butyl 4-(4-methylbenzylidene)piperidine-1-carboxylate (45d)



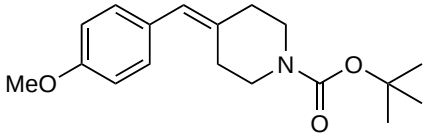
Using General Method 2, **36d** (0.50 g, 2.1 mmol), *N*-Boc-4-piperidone (0.22 g, 1.1 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.30 g, 7.5 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45d** as a white solid (163 mg, 51%). R_f = 0.31 (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{25}NO_2 - C(CH_3)_3$: 232.1338; found 232.1329. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 [9H, s, ^{t}Bu], 2.27-2.37 [5H, m, H(5) + CH_3], 2.41-2.50 [2H, m, H(3)], 3.34-3.43 [2H, m, H(2)], 3.45-3.54 [2H, m, H(6)], 6.32 [1H, s, H(A)], 7.05-7.17 [4H, m, H(2') + H(3') + H(5') + H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.27 [CH_3], 28.61 [^{t}Bu], 29.33 [C(3)], 36.35 [C(5)], 45.28 [br, C(2) + C(6)], 79.65 [^{t}Bu], 124.51 [C(A)], 128.91 [C(2') + C(6')], 129.00 [C(3') + C(5')], 134.65 [C(1')], 136.11 [C(4')], 137.91 [C(4)], 154.92 [C=O].

tert-Butyl 4-(2-methoxybenzylidene)piperidine-1-carboxylate (45e)



Using General Method 2, **36e** (0.57 g, 2.2 mmol), *N*-Boc-4-piperidone (0.22 g, 1.1 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.35 g, 8.8 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45e** as a colourless oil (190 mg, 56%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 [9H, s, ^{t}Bu], 2.30-2.42 [4H, m, H(3) + H(5)], 3.36-3.45 [2H, m, H(2)], 3.48-3.56 [2H, m, H(6)], 3.82 [3H, s, OCH_3], 6.35 [1H, s, H(A)], 6.87 [1H, d, $^3J_{3',4'}$ = 7.8 Hz, H(3')], 6.91 [1H, t, $^3J_{4',5'} = {}^3J_{5',6'}$ = 7.8 Hz, H(5')], 7.11 [1H, dd, $^3J_{5',6'}$ = 7.8 Hz, $^4J_{4',6'}$ = 1.7 Hz, H(6')], 7.21 [1H, td, $^3J_{3',4'} = {}^3J_{4',5'}$ = 7.8 Hz, $^4J_{4',6'}$ = 1.7 Hz, H(4')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.58 [^{t}Bu], 29.66 [C(3)], 36.34 [C(5)], 45.28 [br, C(2) + C(6)], 55.48 [OCH_3], 79.55 [^{t}Bu], 110.57 [C(3')], 120.09 [C(5')], 120.17 [C(1')], 126.32 [C(4')], 128.02 [C(A)], 130.54 [C(6')], 138.45 [C(4)], 154.91 [C=O], 157.19 [C(2')].

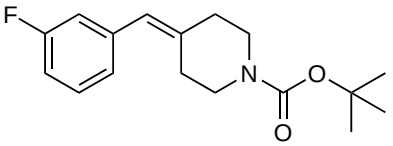
tert-Butyl 4-(4-methoxybenzylidene)piperidine-1-carboxylate (45g)



Using General Method 2, **36g** (0.57 g, 2.2 mmol), *N*-Boc-4-piperidone (0.22 g, 1.1 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.18 g, 4.4 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45g** as a colourless oil (90 mg, 27%). R_f = 0.24 (1:9 ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.24-2.36 [2H, m, H(5)], 2.39-2.50 [2H, m, H(3)], 3.33-3.44 [2H, m, H(2)], 3.45-3.55 [2H, m, H(6)], 3.80 [3H, s, OCH_3], 6.30 [1H, s, H(A)], 6.80-6.91 [2H, m, H(3') + H(5')], 7.07-7.17 [2H, m, H(2') + H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.60 [^{t}Bu], 29.26 [C(3)], 36.30 [C(5)], 45.14 [br, C(2) + C(6)], 55.38 [OCH_3], 79.63 [^{t}Bu], 113.74 [C(3') + C(5')], 124.10 [C(A)], 130.12 [C(2') + C(6')], 137.21 [C(1')], 154.91 [C=O], 158.19 [C(4')].

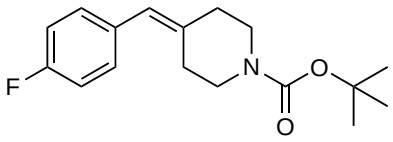
^{1}H NMR data for this compound has been reported previously,[115] but was not consistent with data reported here.

tert-Butyl 4-(3-fluorobenzylidene)piperidine-1-carboxylate (45i)



Using General Method 2, **36i** (0.54 g, 2.2 mmol), *N*-Boc-4-piperidone (0.22 g, 1.1 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.31 g, 7.7 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45i** as a colourless oil (270 mg, 84%). R_f = 0.41 (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{22}FNO_2 - C(CH_3)_3$: 236.1087; found 236.1080. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.25-2.39 [2H, m, H(5)], 2.39-2.54 [2H, m, H(3)], 3.32-3.46 [2H, m, H(2)], 3.46-3.58 [2H, m, H(6)], 6.32 [1H, s, H(A)], 6.86-6.93 [2H, m, H(2') + H(4')], 6.95 [1H, d, $^3J_{5',6'}$ = 7.8 Hz, H(6')], 7.27 [1H, td, $^3J_{4',5'} = {}^3J_{5',6'}$ = 7.8 Hz, $^4J_{H,F}$ = 6.4 Hz, H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.46 [^{t}Bu], 29.22 [C(3)], 36.16 [C(5)], 44.94 [br, C(2) + C(6)], 79.62 [^{t}Bu], 113.18 [d, $^2J_{C,F}$ = 21.5 Hz, C(4')], 115.60 [d, $^2J_{C,F}$ = 21.0 Hz, C(2')], 123.49 [d, $^4J_{C,F}$ = 1.9 Hz, C(A)], 124.61 [d, $^4J_{C,F}$ = 2.9 Hz, C(6')], 129.59 [d, $^3J_{C,F}$ = 8.6 Hz, C(5')], 139.66 [d, $^3J_{C,F}$ = 7.8 Hz, C(1')], 139.71 [C(4)], 154.72 [C=O], 162.69 [d, $^1J_{C,F}$ = 245.1 Hz, C(3')].

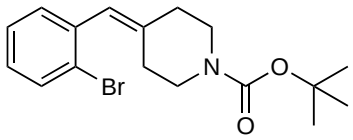
tert-Butyl 4-(4-fluorobenzylidene)piperidine-1-carboxylate (45j)



Using General Method 2, **36j** (0.50 g, 2.0 mmol), *N*-Boc-4-piperidone (0.22 g, 1.1 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.30 g, 7.5 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45j** as a colourless oil (223 mg, 69%). R_f = 0.25 (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{22}FNO_2 - C(CH_3)_3$: 236.1087; found 236.1083. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.25-2.36 [2H, m, H(5)], 2.37-2.47 [2H, m, H(3)], 3.34-3.44 [2H, m, H(2)], 3.45-3.56 [2H, m, H(6)], 6.31 [1H, s, H(A)], 7.96-7.04 [2H, m, H(3') + H(5')], 7.11-7.18 [2H, m, H(2') + H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.46 [^{t}Bu], 29.10 [C(3)], 36.13 [C(5)], 44.98 [br, C(2) + C(6)], 79.59 [^{t}Bu], 115.03 [d, $^2J_{C,F}$ = 21.5 Hz, C(3') + C(5')], 123.44 [C(A)], 130.38 [d, $^3J_{C,F}$ = 7.6 Hz, C(2') + C(6')], 133.38 [d, $^4J_{C,F}$ = 3.3 Hz, C(1')], 138.48 [br, C(4)], 154.75 [C=O], 161.35 [d, $^1J_{C,F}$ = 245.6 Hz, C(4')].

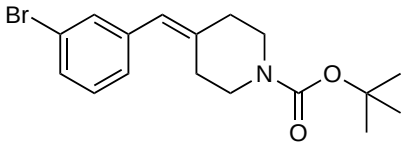
^{1}H NMR data for this compound has been reported previously,[115] but was not consistent with data reported here.

tert-Butyl 4-(2-bromobenzylidene)piperidine-1-carboxylate (45k)



Using General Method 2, **36k** (1.02 g, 3.3 mmol), *N*-Boc-4-piperidone (0.35 g, 1.8 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.26 g, 6.5 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45k** as a white solid (617 mg, 100%). R_f = 0.34 (1:9 ethyl acetate/hexane). MP: 89-90°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{22}{}^{79}BrNO_2/C_{17}H_{22}{}^{81}BrNO_2 - C(CH_3)_3$: 296.0286/298.0266; found 296.0294/298.0276. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 [9H, s, ^{t}Bu], 2.22-2.33 [2H, m, H(5)], 2.32-2.42 [2H, m, H(3)], 3.34-3.45 [2H, m, H(2)], 3.48-3.58 [2H, m, H(6)], 6.31 [1H, s, H(A)], 7.09 [1H, td, $^3J_{3',4'} = {}^3J_{4',5'}$ = 7.7 Hz, $^4J_{4',6'}$ = 1.5 Hz, H(4')], 7.17 [1H, dd, $^3J_{5',6'}$ = 7.7 Hz, $^4J_{4',6'}$ = 1.5 Hz, H(6')], 7.25 [1H, br t‡, $^3J_{4',5'} = {}^3J_{5',6'}$ = 7.7 Hz, H(5')], 7.57 [1H, dd, $^3J_{3',4'}$ = 7.7 Hz, $^4J_{3',5'}$ = 0.9 Hz, H(3')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.61 [^{t}Bu], 29.54 [C(3)], 36.02 [C(5)], 45.24 [br, C(2) + C(6)], 79.73 [^{t}Bu], 124.17 [C(A)], 124.43 [C(2')], 127.04 [C(4')], 128.27 [C(5')], 131.03 [C(6')], 132.70 [C(3')], 137.73 [C(4)], 139.82 [C(1')], 154.88 [C=O].

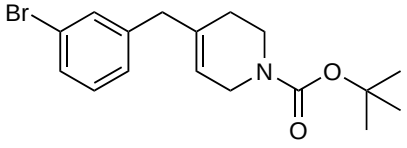
tert-Butyl 4-(3-bromobenzylidene)piperidine-1-carboxylate (45l)



Synthesis method a. Using General Method 2, **36l** (0.75 g, 2.4 mmol), *N*-Boc-4-piperidone (243 mg, 1.22 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.20 g, 5.0 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45l** as a white solid (289 mg, 67%). R_f = 0.27 (1:9 ethyl acetate/hexane). MP: 83-84°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{22}{}^{79}BrNO_2/C_{17}H_{22}{}^{81}BrNO_2 - C(CH_3)_3$: 296.0286/298.0266; found 296.0278/298.0258. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.27-2.37 [2H, m, H(5)], 2.38-2.48 [2H, m, H(3)], 3.36-3.44 [2H, m, H(2)], 3.47-3.56 [2H, m, H(6)], 6.29 [1H, s, H(A)], 7.11 [1H, br d‡, $^3J_{5',6'}$ = 7.7 Hz, H(6')], 7.18 [1H, t, $^3J_{4',5'} = {}^3J_{5',6'}$ = 7.7 Hz, H(5')], 7.29-7.38 [2H, m, H(2') + H(4')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.59 [^{t}Bu], 29.33 [C(3)], 36.27 [C(5)], 45.12 [br, C(2) + C(6)], 79.78 [^{t}Bu], 122.40 [C(3')], 123.31 [C(A)], 127.63 [C(6')], 129.44 [C(5')], 129.82 [C(2')], 131.88 [C(4')], 139.68 [C(1')], 140.11 [C(4)], 154.84 [C=O].

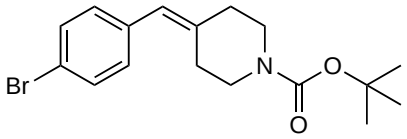
Synthesis method b. *N*-Boc-4-piperidone (100 mg, 0.50 mmol) and **36l** (190 mg, 0.62 mmol) were combined in ethanol (4 mL) with water (1 drop). Potassium hydroxide pellets (0.14 g, 2.50 mmol) were added over 10 minutes. The mixture was stirred at room temperature for 30 min then 70°C for 2 hr, before cooling to 60°C and adding ice water (10 mL). The mixture was extracted with ethyl acetate (3 x 30 mL) and chromatographed on silica gel eluting with 1:9 ethyl acetate/hexane to give an inseparable mixture of products containing mostly recovered reagents. ^{1}H NMR analysis of the crude material indicated the mixture contained **45l** and *tert*-butyl 4-(3-bromobenzyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (**55l**), with an approximate ratio of 5:1 **45l** and **55l**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 [1.35H, s, *^{t}Bu], 1.48 [7.65H, s, ^{t}Bu], 1.97 [0.3H, br s, *H(5)], 2.26-2.38 [1.7H, m, H(5)], 2.38-2.48 [1.7H, m, H(3)], 3.27 [0.3H, br s, *H(A)], 3.35-3.57 [3.7H, m, H(2) + H(6) + *H(6)], 3.89 [0.3H, br s‡, *H(2)], 5.40 [0.15H, br s‡, *H(3)], 6.29 [0.85H, s, H(A)], 7.03-7.23 [2H, m, H(5') + H(6') + *H(5') + *H(6')], 7.28-7.40 [2H, m, H(2') + H(4') + *H(2') + *H(4')].

* corresponds to minor product **55l**.



55l

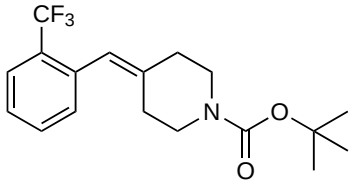
tert-Butyl 4-(4-bromobenzylidene)piperidine-1-carboxylate (45m)



Using General Method 2, **36m** (0.75 g, 2.4 mmol), *N*-Boc-4-piperidone (243 mg, 1.22 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.20 g, 5.0 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45m** as a white solid (301 mg, 70%). R_f = 0.40 (1:9 ethyl acetate/hexane). MP: 66-67°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{22}{}^{79}BrNO_2/C_{17}H_{22}{}^{81}BrNO_2 - C(CH_3)_3$: 296.0286/298.0266; found 296.0278/298.0258. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.24-2.37 [2H, m, H(5)], 2.36-2.48 [2H, m, H(3)], 3.33-3.44 [2H, m, H(2)], 3.45-3.56 [2H, m, H(6)], 6.28 [1H, s, H(A)], 7.00-7.09 [2H, m, H(3') + H(5')], 7.38-7.47 [2H, m, H(2') + H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.37 [^{t}Bu], 29.62 [C(3)], 36.12 [C(5)], 44.98 [br, C(2) + C(6)], 79.54 [^{t}Bu], 120.06 [C(4')], 123.33 [C(A)], 130.43 [C(2') + C(6')], 131.19 [C(3') + C(5')], 136.20 [C(1')], 139.27 [C(4)], 154.63 [C=O].

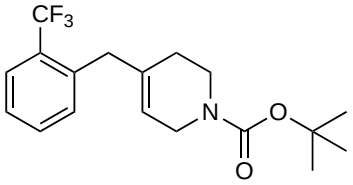
This data is consistent with that reported in literature.[70]

tert-Butyl 4-(2-trifluoromethylbenzylidene)piperidine-1-carboxylate (45n)



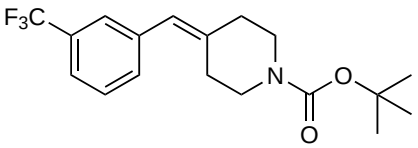
Using General Method 2, **36n** (0.33 g, 2.2 mmol), *N*-Boc-4-piperidone (0.22 g, 1.1 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.35 g, 8.8 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45n** as a white solid (310 mg, 82%). R_f = 0.21 (1:9 ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 [9H, s, ^{t}Bu], 2.13-2.25 [2H, m, H(5)], 2.29-2.41 [2H, m, H(3)], 3.30-3.42 [2H, m, H(2)], 3.46-3.57 [2H, m, H(6)], 6.50 [1H, s, H(A)], 7.20 [1H, d, $^3J_{5',6'}$ = 7.6 Hz, H(6')], 7.33 [1H, t, $^3J_{3',4'} = {}^3J_{4',5'}$ = 7.6 Hz, H(4')], 7.47 [1H, t, $^3J_{4',5'} = {}^3J_{5',6'}$ = 7.6 Hz, H(5')], 7.65 [1H, d, $^3J_{3',4'}$ = 7.6 Hz, H(3')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.45 [^{t}Bu], 29.52 [C(3)], 36.00 [C(5)], 45.14 [br, C(2) + C(6)], 79.59 [^{t}Bu], 121.17 [C(A)], 124.24 [q, $^1J_{C,F}$ = 273.8 Hz, CF_3], 125.76 [q, $^3J_{C,F}$ = 5.4 Hz, C(3')], 126.66 [C(4')], 128.80 [q, $^2J_{C,F}$ = 29.3 Hz, C(2')], 131.33 [C(5')], 131.42 [C(6')], 136.38 [C(1')], 140.45 [C(4)], 154.74 [C=O].

Synthesis method b. *N*-Boc-4-piperidone (100 mg, 0.50 mmol) and **36n** (180 mg, 0.62 mmol) were combined in ethanol (4 mL) with water (1 drop). Potassium hydroxide pellets (0.14 g, 2.50 mmol) were added over 10 minutes. The mixture was stirred at room temperature for 30 min then 70°C for 2 hr, before cooling to 60°C and adding ice water (10 mL). The mixture was extracted with ethyl acetate (3 x 30 mL) and chromatographed on silica gel eluting with 1:9 ethyl acetate/hexane to give an inseparable mixture containing mostly recovered reagents. ^{1}H NMR analysis of the material indicated the mixture contained **45n** and *tert*-butyl 4-(2-(trifluoromethyl)benzyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (**55n**), with an approximate ratio of 49:1 **45n** and **55n**.



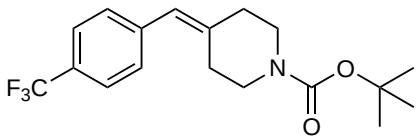
55n

tert-Butyl 4-(3-trifluoromethylbenzylidene)piperidine-1-carboxylate (45o)



Using General Method 2, **36o** (0.65 g, 2.2 mmol), *N*-Boc-4-piperidone (220 mg, 1.1 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.35 g, 8.8 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45o** as a colourless oil (223 mg, 59%). R_f = 0.32 (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{22}F_3NO_2 - C(CH_3)_3$: 286.1055; found 286.1051. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.30-2.39 [2H, m, H(5)], 2.40-2.48 [2H, m, H(3)], 3.37-3.46 [2H, m, H(2)], 3.48-3.57 [2H, m, H(6)], 6.37 [1H, s, H(A)], 7.36 [1H, d, $^3J_{5',6'} = 7.6$ Hz, H(6')], 7.40-7.50 [3H, m, H(2') + H(4') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.56 [^{t}Bu], 29.29 [br, C(3)], 36.27 [br, C(5)], 45.03 [br, C(2) + C(6)], 79.80 [^{t}Bu], 123.14 [q, $^3J_{C,F} = 3.8$ Hz, C(2')], 123.38 [C(A)], 124.27 [q, $^1J_{C,F} = 272.3$ Hz, CF_3], 125.68 [q, $^3J_{C,F} = 3.8$ Hz, C(4')], 128.73 [C(5')], 130.73 [q, $^2J_{C,F} = 32.0$ Hz, C(3')], 132.23 [C(6')], 138.25 [C(1')], 140.44 [C(4)], 154.83 [C=O].

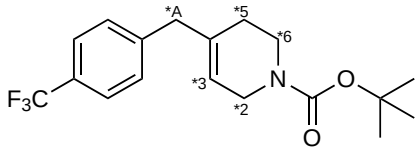
tert-Butyl 4-(4-trifluoromethylbenzylidene)piperidine-1-carboxylate (45p)



Synthesis method a. Using General Method 2, **36p** (0.75 g, 2.5 mmol), *N*-Boc-4-piperidone (0.25 g, 1.3 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.40 g, 10.0 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography on silica gel eluting with 1:19 ethyl acetate/hexane to give **45p** as a colourless oil (242 mg, 57%). R_f = 0.31 (1:9 ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.29-2.39 [2H, m, H(5)], 2.40-2.50 [2H, m, H(3)], 3.35-3.45 [2H, m, H(2)], 3.48-3.58 [2H, m, H(6)], 6.37 [1H, s, H(A)], 7.26-7.32 [2H, m, H(2') + H(6')], 7.53-7.61 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.59 [^{t}Bu], 29.39 [br, C(3)], 36.39 [br, C(5)], 45.18 [br, C(2) + C(6)], 79.84 [^{t}Bu], 123.53 [C(A)], 124.38 [q, $^1J_{C,F}$ = 272.3 Hz, CF_3], 125.26 [q, $^3J_{C,F}$ = 3.8 Hz, C(3') + C(5')], 128.51 [q, $^2J_{C,F}$ = 32.5 Hz, C(4')], 129.24 [C(2') + C(6')], 140.86 [C(1')], 141.22 [br, C(4)], 154.85 [C=O].

^{1}H NMR data for this compound has been reported previously,[115] but was inconsistent with data obtained in this work.

Synthesis method b. *N*-Boc-4-piperidone (200 mg, 0.10 mmol) and **36p** (0.37 g, 1.24 mmol) were combined in ethanol (4 mL) with water (1 drop). Potassium hydroxide pellets (0.28 g, 5.0 mmol) were added over 10 minutes. The mixture was stirred at room temperature for 30 min then 70°C for 2 hr, before cooling to 60°C and adding ice water (10 mL). The mixture was extracted with ethyl acetate (3 x 30 mL) to give an inseparable mixture of **45p** and *tert*-butyl 4-(4-(trifluoromethyl)benzyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (**55p**) as a white solid (134 mg, 39%). ^{1}H NMR analysis indicated the mixture contained approximately a 1:3 ratio of **45p** and **55p**.



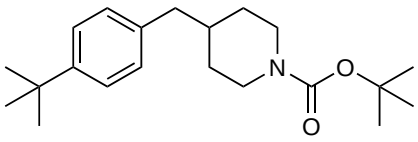
55p

tert-*butyl 4-(4-(trifluoromethyl)benzyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (**55p**) and* tert-*Butyl 4-(4-trifluoromethylbenzylidene)piperidine-1-carboxylate (**45p**):* R_f = 0.30 (1:9 ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 [6.75H, s, *^{t}Bu], 1.48 [2.25H, s, ^{t}Bu], 1.98 [1.5H, br s‡, *H(5)], 2.29-2.39 [0.5H, m, H(5)], 2.40-2.50 [0.5H, m, H(3)], 3.33-3.48 [3.5H, m, H(2) + *H(A) + *H(6)], 3.48-3.58 [0.5H, m, H(6)], 3.89 [1.5H, br s‡, *H(2)], 5.40

[0.75H, br s‡, *H(3)], 6.37 [0.25H, s, H(A)], 7.24-7.32 [2H, m, H(2') + H(6') + *H(2') + *H(6')], 7.51-7.61 [2H, m, H(3') + H(5') + *H(3') + *H(5')].

* Denotes signal corresponding to side-product **55p**.

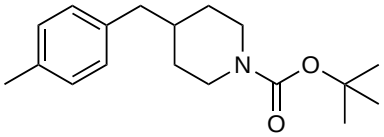
***tert*-Butyl 4-(4-(*tert*-butyl)benzyl)piperidine-1-carboxylate (48a)**



Using General Method 3, **45a** (152 mg, 0.46 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up gave crude **48a** as a colourless oil, which was used without further purification (151 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08-1.19 [2H, m, H(3_{ax}) + H(5_{ax})], 1.31 [9H, s, ^{t}Bu], 1.45 [9H, s, ^{t}Bu], 1.47-1.70 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.49 [2H, d, $^{3}J_{4ax,A} = 6.9$ Hz, H(A)], 2.64 [2H, br t‡, $^{2}J_{(2/6)ax,(2/6)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = 12.9$ Hz, H(2_{ax}) + H(6_{ax})], 3.02-3.10 [2H, m, H(2_{eq}) + H(6_{eq})], 7.04-7.09 [2H, m, H(2'') + H(6'')], 7.27-7.32 [2H, m, H(3'') + H(5'')].

This data is consistent with that reported in literature.[116]

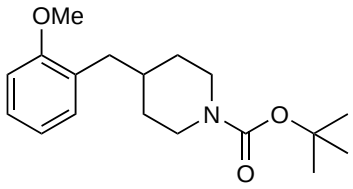
***tert*-Butyl 4-(4-methylbenzyl)piperidine-1-carboxylate (48d)**



Using General Method 3, **45d** (163 mg, 0.57 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up gave crude **48d** as a colourless oil which was used without further purification (164 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{27}NO_2 - C(CH_3)_3$: 234.1494; found 234.1490. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 12.2$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 3.3$ Hz, H(3_{ax}) + H(5_{ax})], 1.45 [9H, s, ^{t}Bu], 1.56-1.69 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.32 [3H, s, CH_3], 2.49 [2H, d, $^{3}J_{4ax,A} = 6.8$ Hz, H(A)], 2.63 [2H, br t‡, $^{2}J_{(2/6)ax,(2/6)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = 12.2$ Hz, H(2_{ax}) + H(6_{ax})], 3.95-4.17 [2H, m, H(2_{eq}) + H(6_{eq})], 7.00-7.05 [2H, m, H(2') + H(6')], 7.06-7.12 [2H, m, H(3') + H(5')].

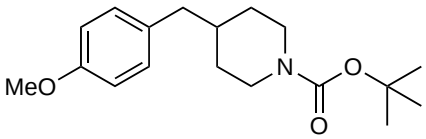
This data is consistent with that reported in literature.[117]

tert-Butyl 4-(2-methoxybenzyl)piperidine-1-carboxylate (48e)



Using General Method 3, **45e** (190 mg, 0.63 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up gave **48e** as a colourless oil which was used without further purification (192 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{27}NO_3 - C(CH_3)_3$: 250.1443; found 250.1443. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.2$ Hz, $^3J_{(2/6)eq,(3/5)ax} = 3.7$ Hz, H(3_{ax}) + H(5_{ax})], 1.45 [9H, s, ^{t}Bu], 1.60 [2H, br d‡, $^2J_{(3/5)ax,(3/5)eq} = 12.1$ Hz, H(3_{eq}) + H(5_{eq})], 1.70 [1H, ttt, $^3J_{(3/5)ax,4ax} = 12.1$ Hz, $^3J_{4ax,A} = 7.1$ Hz, $^3J_{(3/5)eq,4ax} = 3.7$ Hz, H(4_{ax})], 2.54 [2H, d, $^3J_{4ax,A} = 7.1$ Hz, H(A)], 2.64 [2H, br t‡, $^2J_{(2/6)ax,(2/6)eq} = {}^3J_{(2/6)ax,(3/5)ax} = 12.2$ Hz, H(2_{ax}) + H(6_{ax})], 3.81 [3H, s, OCH_3], 3.96-4.12 [2H, m, H(2_{eq}) + H(6_{eq})], 6.82-6.90 [2H, m, H(3') + H(5')], 7.06 [1H, br dd‡, $^3J_{5',6'} = 7.8$ Hz, $^4J_{4',6'} = 1.6$ Hz, H(6')], 7.18 [1H, td, $^3J_{3',4'} = {}^3J_{4',5'} = 7.8$ Hz, $^4J_{4',6'} = 1.6$ Hz, H(4')].

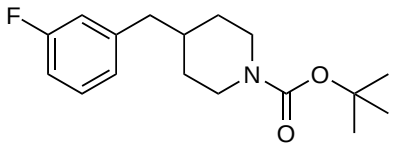
tert-Butyl 4-(4-methoxybenzyl)piperidine-1-carboxylate (48g)



Using General Method 3, **45g** (105 mg, 0.35 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up gave **48g** as a colourless oil (106 mg, 100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 [2H, br q‡, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.2$ Hz, H(3_{ax}) + H(5_{ax})], 1.45 [9H, s, ^{t}Bu], 1.55-1.67 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.47 [2H, d, $^3J_{4ax,A} = 6.7$ Hz, H(A)], 2.63 [2H, br t‡, $^2J_{(2/6)ax,(2/6)eq} = {}^3J_{(2/6)ax,(3/5)ax} = 11.0$ Hz, H(2_{ax}) + H(6_{ax})], 3.79 [3H, s, OCH_3], 3.94-4.23 [2H, m, H(2_{eq}) + H(6_{eq})], 6.79-6.86 [2H, m, H(3') + H(5')], 7.01-7.08 [2H, m, H(2') + H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.62 [^{t}Bu], 32.09 [br, C(3) + C(5)], 38.48 [C(4)], 42.36 [C(A)], 44.14 [br, C(2) + C(6)], 55.38 [OCH_3], 79.33 [^{t}Bu], 113.77 [C(3') + C(5')], 130.11 [C(2') + C(6')], 132.43 [C(1')], 155.01 [C=O], 158.01 [C(4')].

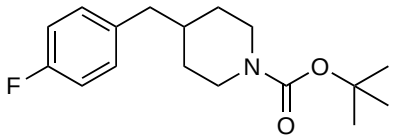
This data is consistent with that reported previously.[118]

tert-Butyl 4-(3-fluorobenzyl)piperidine-1-carboxylate (48i)



Using General Method 3, **45i** (260 mg, 0.89 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up gave **48i** as a colourless oil (261 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{24}FNO_2 - C(CH_3)_3$: 238.1243; found 238.1234. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.5$ Hz, $^3J_{(3/5)ax,(2/6)eq} = 4.4$ Hz, $H(3_{ax}) + H(5_{ax})$], 1.45 [9H, s, ^{t}Bu], 1.54-1.72 [3H, m, $H(3_{eq}) + H(4_{ax}) + H(5_{eq})$], 2.53 [2H, d, $^3J_{4ax,A} = 7.1$ Hz, H(A)], 2.64 [2H, br t‡, $^2J_{(2/6)ax,(2/6)eq} = {}^3J_{(2/6)ax,(3/5)ax} = 12.5$ Hz, $H(2_{ax}) + H(6_{ax})$], 4.08 [2H, br s‡, $H(2_{eq}) + H(6_{eq})$], 6.81-6.93 [3H, m, H(2') + H(4') + H(6')], 7.23 [1H, td, $^3J_{4',5'} = {}^3J_{5',6'} = 7.8$ Hz, $^4J_{H,F} = 6.1$ Hz, H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.12 [^{t}Bu], 34.57 [br, C(3) + C(5)], 40.66 [C(4)], 45.50 [d, $^4J_{C,F} = 1.4$ Hz, C(A)], 46.46 [br, C(2) + C(6)], 81.93 [^{t}Bu], 115.48 [d, $^2J_{C,F} = 21.0$ Hz, C(4)], 118.48 [d, $^2J_{C,F} = 20.5$ Hz, C(2')], 127.40 [d, $^4J_{C,F} = 2.9$ Hz, C(6')], 132.26 [d, $^3J_{C,F} = 8.6$ Hz, C(5')], 145.45 [d, $^3J_{C,F} = 6.7$ Hz, C(1')], 157.48 [C=O], 165.48 [d, $^1J_{C,F} = 245.1$ Hz, C(3')].

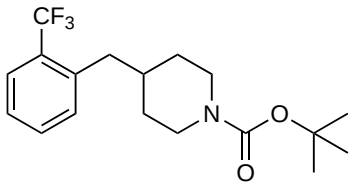
tert-Butyl 4-(4-fluorobenzyl)piperidine-1-carboxylate (48j)



Using General Method 3, **45j** (223 mg, 0.76 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up gave **48j** as a colourless oil which was used without further purification (224 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{24}FNO_2 - C(CH_3)_3$: 238.1243; found 238.1239. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.0$ Hz, $^3J_{(3/5)ax,(2/6)eq} = 3.0$ Hz, $H(3_{ax}) + H(5_{ax})$], 1.45 [9H, s, ^{t}Bu], 1.52-1.72 [3H, m, $H(3_{eq}) + H(4_{ax}) + H(5_{eq})$], 2.50 [2H, d, $^3J_{4ax,A} = 7.1$ Hz, H(A)], 2.63 [2H, br t‡, $^2J_{(2/6)ax,(2/6)eq} = {}^3J_{(2/6)ax,(3/5)ax} = 12.0$ Hz, $H(2_{ax}) + H(6_{ax})$], 4.07 [2H, br s‡, $H(2_{eq}) + H(6_{eq})$], 6.93-6.99 [2H, m, H(3') + H(5')], 7.05-7.11 [2H, m, H(2') + H(6')].

This data is consistent with that reported previously.[119]

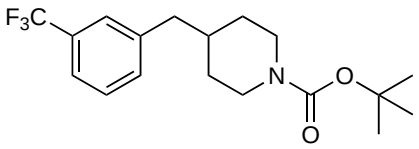
tert-Butyl 4-(2-trifluoromethylbenzyl)piperidine-1-carboxylate (48n)



Using General Method 3, **45n** (310 mg, 0.91 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up gave **48n** as a colourless oil which was used without further purification (312 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{24}F_3NO_2 - C(CH_3)_3$: 288.1211; found 288.1206. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.3$ Hz, $^3J_{(3/5)ax,(2/6)eq} = 4.0$ Hz, H(3_{ax}) + H(5_{ax})], 1.46 [9H, s, ^{t}Bu], 1.61 [2H, br d‡, $^2J_{(3/5)ax,(3/5)eq} = 12.3$ Hz, H(3_{eq}) + H(5_{eq})], 1.74 [1H, ttt, $^3J_{(3/5)ax,4ax} = 12.3$ Hz, $^3J_{4ax,A} = 7.1$ Hz, $^3J_{(3/5)eq,4ax} = 3.7$ Hz, H(4_{ax})], 2.62 [2H, br t‡, $^2J_{(2/6)ax,(2/6)eq} = {}^3J_{(2/6)ax,(3/5)ax} = 12.3$ Hz, H(2_{ax}) + H(6_{ax})], 2.72 [2H, d, $^3J_{4ax,A} = 7.1$ Hz, H(A)], 4.09 [2H, br s‡, H(2_{eq}) + H(6_{eq})], 7.25-7.33 [2H, m, H(4') + H(6')], 7.46 [1H, br t‡, $^3J_{4',5'} = {}^3J_{5',6'} = 7.4$ Hz, H(5')], 7.63 [1H, br d‡, $^3J_{3',4'} = 7.8$ Hz, H(3')].

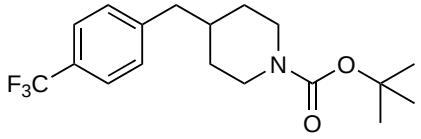
This data is consistent with that reported in literature.[116]

tert-Butyl 4-(3-trifluoromethylbenzyl)piperidine-1-carboxylate (48o)



Using General Method 3, **45o** (223 mg, 0.65 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up and column chromatography on silica gel eluting with 9:1 hexane/ethyl acetate gave **48o** as a colourless oil (224 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{14}H_{16}F_3NO_2 - C(CH_3)_3$: 288.1211; found 288.1206. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.0$ Hz, $^3J_{(3/5)ax,(2/6)eq} = 3.4$ Hz, H(3_{ax}) + H(5_{ax})], 1.45 [9H, s, ^{t}Bu], 1.55-1.74 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.50-2.77 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 4.09 [2H, br s‡, H(2_{eq}) + H(6_{eq})], 7.31 [1H, br d‡, $^3J_{5',6'} = 8.0$ Hz, H(6')], 7.42-7.49 [2H, m, H(2') + H(5')], 7.46 [1H, br d‡, $^3J_{4',5'} = 8.0$ Hz, H(4')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.60 [^{t}Bu], 32.03 [br, C(3) + C(5)], 38.19 [C(4)], 43.07 [C(A)], 43.97 [br, C(2) + C(6)], 79.46 [^{t}Bu], 123.04 [q, $^3J_{C,F} = 3.8$ Hz, C(4')], 124.36 [q, $^1J_{C,F} = 272.3$ Hz, CF_3], 125.81 [q, $^3J_{C,F} = 3.8$ Hz, C(2')], 128.80 [C(6')], 130.77 [q, $^2J_{C,F} = 32.0$ Hz, C(3')], 132.62 [q, $^4J_{C,F} = 1.0$ Hz, C(5')], 141.24 [C(1')], 154.96 [C=O].

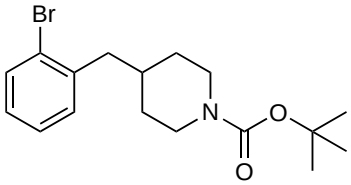
tert-Butyl 4-(4-trifluoromethylbenzyl)piperidine-1-carboxylate (48p)



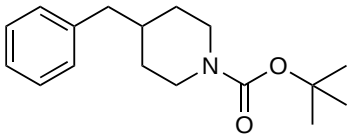
Using General Method 3, **45p** (232 mg, 0.68 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up gave **48p** as a colourless oil (215 mg, 92%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{24}F_3NO_2 - C(CH_3)_3$: 288.1211; found 288.1205. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.1$ Hz, $^3J_{(3/5)ax,(2/6)eq} = 3.7$ Hz, $H(3_{ax}) + H(5_{ax})$], 1.45 [9H, s, ^{t}Bu], 1.54-1.75 [3H, m, $H(3_{eq}) + H(4_{ax}) + H(5_{eq})$], 2.54-2.73 [4H, m, $H(A) + H(2_{ax}) + H(6_{ax})$], 4.08 [2H, br s‡, $H(2_{eq}) + H(6_{eq})$], 7.21-7.27 [2H, m, H(2') + H(6')], 7.51-5.57 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.60 [^{t}Bu], 32.04 [br, C(3) + C(5)], 38.16 [C(4)], 43.07 [C(A)], 44.16 [br, C(2) + C(6)], 79.47 [^{t}Bu], 124.46 [q, $^1J_{C,F} = 271.73$ Hz, CF_3], 125.32 [q, $^3J_{C,F} = 3.8$ Hz, C(3') + C(5')], 128.52 [q, $^2J_{C,F} = 32.4$ Hz, C(4')], 129.51 [C(2') + C(6')], 144.48 [br‡, C(1')], 154.96 [C=O].

^{1}H NMR data for this compound has been reported previously,[115] but was not consistent with data reported here.

tert-Butyl 4-(2-bromobenzyl)piperidine-1-carboxylate (48k)



Using General Method 3, **45k** (20 mg, 0.06 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up gave **48x** as an orange oil (20 mg, 98%).



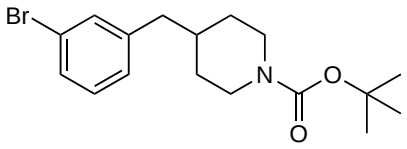
48x

tert-*Butyl 4-benzylpiperidine-1-carboxylate (**48x**):* $R_f = 0.39$ (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{25}NO_2 - C(CH_3)_3$: 220.1338; found 220.1337. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax}$

= 12.0 Hz, $^{3}J_{(3/5)ax,(2/6)eq}$ = 3.6 Hz, H(3_{ax}) + H(5_{ax})], 1.45 [9H, s, ^{t}Bu], 1.55-1.72 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.53 [2H, d, $^{3}J_{4ax,A}$ = 7.0 Hz, H(A)], 2.63 [2H, br t‡, $^{2}J_{(2/6)ax,(2/6)eq}$ = $^{3}J_{(2/6)ax,(3/5)ax}$ = 12.0 Hz, H(2_{ax}) + H(6_{ax})], 4.07 [2H, br s‡, H(2_{eq}) + H(6_{eq})], 7.10-7.15 [2H, m, H(2') + H(6')], 7.19 [1H, t, $^{3}J_{3',4'}$ = $^{3}J_{4'/5'}$ = 7.4 Hz, H(4')], 7.24-7.30 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.62 [^{t}Bu], 32.13 [br, C(3) + C(5)], 38.32 [C(4)], 43.29 [C(A)], 43.95 [br, C(2) + C(6)], 79.34 [^{t}Bu], 126.07 [C(4')], 128.37 [C(3') + C(5')], 129.25 [C(2') + C(6')], 140.37 [C(1')], 155.01 [C=O].

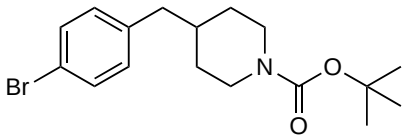
This data is consistent with that reported previously.[69]

tert-Butyl 4-(3-bromobenzyl)piperidine-1-carboxylate (48l)



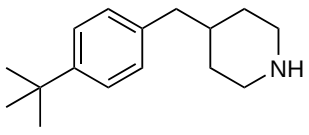
Using General Method 3, **45l** (20 mg, 0.06 mmol) in methanol (30 mL) was treated with Pd-C catalyst under a hydrogen atmosphere for 2 hr. Work-up gave **48x** as an orange oil (20 mg, 98%). Data as above.

tert-Butyl 4-(4-bromobenzyl)piperidine-1-carboxylate (48m)



Using General Method 3, **45m** (310 mg, 0.91 mmol) in methanol (30 mL) was treated with Pd-C catalyst under a hydrogen atmosphere for 2 hr. Work-up gave **48x** as an orange oil (311 mg, 100%). Data as above.

4-(4-_tert_-Butylbenzyl)piperidine (31a)

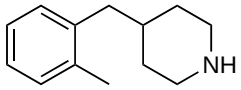


Synthesis method a. Using General Method 4, **48a** (148 mg, 0.45 mmol) in dichloromethane (8 mL) was treated with trifluoroacetic acid (2 mL) to give **31a** as a yellow oil (103 mg, 100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq}$ = $^{3}J_{(2/6)ax,(3/5)ax}$ = $^{3}J_{(3/5)ax,4ax}$ = 12.2 Hz, $^{3}J_{(2/6)eq,(3/5)ax}$ = 2.3 Hz, H(3_{ax}) + H(5_{ax})], 1.32 [9H, s, ^{t}Bu], 1.60-1.71 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.51 [2H, d, $^{3}J_{4ax,A}$ = 6.7 Hz, H(A)], 2.57 [2H, td,

$^{2}J_{(2/6)ax,(2/6)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = 12.2$ Hz, $^{3}J_{(2/6)ax,(3/5)eq} = 2.0$ Hz, H(2_{ax}) + H(6_{ax})], 3.04 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq} = 12.2$ Hz, H(2_{eq}) + H(6_{eq})], 7.02-7.09 [2H, m, H(2') + H(6')], 7.26-7.31 [2H, m, H(3') + H(5')]. ^{13}C NMR (500 MHz, $CDCl_3$): δ 31.58 [^{t}Bu], 32.15 [C(3) + C(5)], 38.25 [C(4)], 42.81 [C(A)], 45.93 [C(2) + C(6)], 85.14 [^{t}Bu], 125.15 [C(3') + C(5')], 125.28 [C(1')], 128.90 [C(2') + C(6')], 148.65 [C(4')].

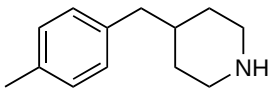
Synthesis method b. Using General Method 6, **49a** (98 mg, 0.37 mmol) and saturated aqueous sodium bicarbonate solution (10 mL) were reacted in dichloromethane (10 mL) to give **31a** as a yellow oil (67 mg, 79%). Data as above.

4-(2-Methylbenzyl)piperidine (31b)



Using General Method 6, **49b** (118 mg, 0.52 mmol) and saturated aqueous sodium bicarbonate solution (10 mL) were reacted in dichloromethane (10 mL) to give **31b** as a yellow oil (69 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 11.8$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 3.1$ Hz, H(3_{ax}) + H(5_{ax})], 1.55-1.70 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 1.94 [1H, br s, NH], 2.30 [3H, s, CH_3], 2.47-2.62 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.05 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq} = 11.8$ Hz, H(2_{eq}) + H(6_{eq})], 7.04-7.17 [4H, m, H(3') + H(4') + H(5') + H(6')].

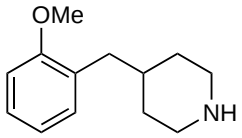
4-(4-Methylbenzyl)piperidine (31d)



Synthesis method a. Using General Method 6, **49d** (137 mg, 0.61 mmol) and saturated aqueous sodium bicarbonate solution (10 mL) were reacted in dichloromethane (10 mL) to give **31d** as a yellow oil (47 mg, 41%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 12.5$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 3.2$ Hz, H(3_{ax}) + H(5_{ax})], 1.60-1.77 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.32 [3H, s, CH_3], 2.51 [2H, d, $^{3}J_{4ax,A} = 7.0$ Hz, H(A)], 2.63 [2H, td, $^{2}J_{(2/6)ax,(2/6)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = 12.5$ Hz, $^{3}J_{(2/6)ax,(3/5)eq} = 3.2$ Hz, H(2_{ax}) + H(6_{ax})], 3.16 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq} = 12.5$ Hz, H(2_{eq}) + H(6_{eq})], 4.57 [1H, br s, NH], 7.00-7.04 [2H, m, H(2') + H(6')], 7.06-7.11 [2H, m, H(3') + H(5')].

Synthesis method b. Using General Method 4, **48d** (164 mg, 0.57 mmol) and trifluoroacetic acid (2 mL) were reacted in dichloromethane (8 mL) to give **31d** as a yellow oil (107 mg, 100%). Data as above.

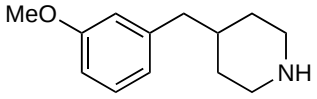
4-(2-Methoxybenzyl)piperidine (31e)



Synthesis method a. Using General Method 6, **49e** (110 mg, 0.45 mmol) and saturated aqueous sodium bicarbonate solution (10 mL) were reacted in dichloromethane (10 mL) to give **31e** as a yellow oil (79 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.17 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 12.2$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 3.8$ Hz, H(3_{ax}) + H(5_{ax})], 1.54-1.74 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 1.89 [1H, br s, NH], 2.46-2.61 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.04 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq} = 12.2$ Hz, H(2_{eq}) + H(6_{eq})], 3.81 [3H, s, OCH_3], 6.81-6.90 [2H, m, H(3') + H(5')], 7.07 [1H, d, $^{3}J_{5',6'} = 7.5$ Hz, H(6')], 7.18 [1H, t, $^{3}J_{3',4'} = {}^{3}J_{4',5'} = 7.5$ Hz, H(4')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 33.55 [C(3) + C(5)], 36.73 [C(4)], 37.78 [C(A)], 46.73 [C(2) + C(6)], 55.25 [OCH_3], 110.28 [C(3')], 120.06 [C(5')], 127.01 [C(4')], 129.00 [C(1')], 130.93 [C(6')], 157.65 [C(2')].

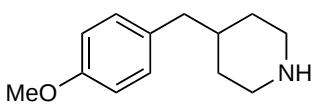
Synthesis method b. Using General Method 4, **48e** (192 mg, 0.63 mmol) and trifluoroacetic acid (2 mL) were reacted in dichloromethane (8 mL) to give **31e** as a pale orange oil (129 mg, 100%). Data as above.

4-(3-Methoxybenzyl)piperidine (31f)



Using General Method 6, **49f** (123 mg, 0.51 mmol) in dichloromethane (10 mL) was treated with saturated aqueous sodium bicarbonate solution (10 mL) to give **31f** as a yellow oil (96 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 12.3$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 3.9$ Hz, H(3_{ax}) + H(5_{ax})], 1.56-1.69 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.04 [1H, br s, NH], 2.41-2.62 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.04 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq} = 12.3$ Hz, H(2_{eq}) + H(6_{eq})], 3.79 [3H, s, OCH_3], 6.66-6.77 [3H, m, H(2') + H(4') + H(6')], 7.18 [1H, t, $^{3}J_{4',5'} = {}^{3}J_{5',6'} = 7.8$ Hz, H(5')].

4-(4-Methoxybenzyl)piperidine (31g)



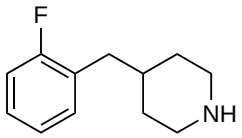
Synthesis method a. Using General Method 6, **49g** (140 mg, 0.58 mmol) and saturated aqueous sodium bicarbonate solution (10 mL) were reacted in dichloromethane (10 mL) to

give **31g** as a yellow oil (91 mg, 77%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{13}H_{19}NO$: 206.1545; found 206.1536. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.52 [2H, qd, $^2J_{(3/5)ax,(3/5)eq}$ = $^3J_{(2/6)ax,(3/5)ax}$ = $^3J_{(3/5)ax,4ax}$ = 12.0 Hz, $^3J_{(2/6)eq,(3/5)ax}$ = 3.7 Hz, H(3_{ax}) + H(5_{ax})], 1.71 [1H, ttt, $^3J_{3ax,4ax}$ = $^3J_{4ax,5ax}$ = 12.0 Hz, $^3J_{4ax,A}$ = 7.3 Hz, $^3J_{3eq,4ax}$ = $^3J_{4ax,5eq}$ = 3.6 Hz, H(4_{ax})], 1.80 [2H, br d‡, $^2J_{(3/5)ax,(3/5)eq}$ = 12.0 Hz, H(3_{eq}) + H(5_{eq})], 2.53 [2H, d, $^3J_{4ax,A}$ = 7.3 Hz, H(A)], 2.78 [2H, td, $^2J_{(2/6)ax,(2/6)eq}$ = $^3J_{(2/6)ax,(3/5)ax}$ = 12.0 Hz, $^3J_{(2/6)ax,(3/5)eq}$ = 1.9 Hz, H(2_{ax}) + H(6_{ax})], 3.34 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq}$ = 12.0 Hz, H(2_{eq}) + H(6_{eq})], 3.79 [3H, s, OCH_3], 6.78-6.90 [2H, m, H(3') + H(5')], 7.00-7.11 [2H, m, H(2') + H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.99 [C(3) + C(5)], 36.67 [C(4)], 41.69 [C(A)], 44.32 [C(2) + C(6)], 55.40 [OCH_3], 114.02 [C(3') + C(5')], 130.05 [C(2') + C(6')], 131.19 [C(1')], 158.30 [C(4')].

^{1}H NMR data for this compound has been reported previously,[120,121] but was not consistent with data reported here.

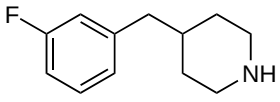
Synthesis method b. Using General Method 4, **48g** (106 mg, 0.35 mmol) and trifluoroacetic acid (1 mL) were reacted in dichloromethane (4 mL) to give **31g** as a yellow oil (71 mg, 100%). Data as above.

4-(2-Fluorobenzyl)piperidine (31h)



Using General Method 6, **49h** (120 mg, 0.52 mmol) and saturated aqueous sodium bicarbonate solution (10 mL) were reacted in dichloromethane (10 mL) to give **31i** as a yellow oil (66 mg, 66%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{12}H_{16}FN$: 194.1345; found 194.1341. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32-1.45 [2H, m, H(3_{ax}) + H(5_{ax})], 1.67-1.82 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.54-2.71 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.20 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq}$ = 12.4 Hz, H(2_{eq}) + H(6_{eq})], 4.77 [1H, br s, NH], 6.96-7.23 [4H, m, H(3') + H(4') + H(5') + H(6')].

4-(3-Fluorobenzyl)piperidine (31i)



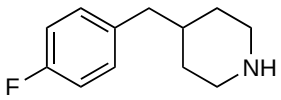
Synthesis method a. Using General Method 6, **49i** (107 mg, 0.47 mmol) and saturated aqueous sodium bicarbonate solution (10 mL) were reacted in dichloromethane (10 mL) to give **31i** as a yellow oil (61 mg, 68%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{12}H_{16}FN$: 194.1345; found 194.1341. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 [2H, qd, $^2J_{(3/5)ax,(3/5)eq}$ =

$^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 12.2$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 3.0$ Hz, H(3_{ax}) + H(5_{ax})], 1.46-1.75 [4H, m, NH + H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.42-2.61 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.04 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq} = 12.2$ Hz, H(2_{eq}) + H(6_{eq})], 6.80-6.95 [3H, m, H(2') + H(4') + H(6')], 7.22 [1H, td, $^{3}J_{4',5'} = {}^{3}J_{5',6'} = 7.5$ Hz, $^{4}J_{5',F} = 6.7$ Hz, H(5')].

This data is consistent with that reported previously.[122]

Synthesis method b. Using General Method 4, **48i** (261 mg, 0.89 mmol) and trifluoroacetic acid (3 mL) were reacted in dichloromethane (12 mL) to give **31i** as a clear oil (162 mg, 94%). Data as above.

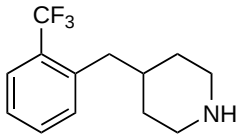
4-(4-Fluorobenzyl)piperidine (31j)



Synthesis method a. Using General Method 6, **49j** (150 mg, 0.65 mmol) and saturated aqueous sodium bicarbonate solution (10 mL) were reacted in dichloromethane (10 mL) to give **31j** as a yellow oil (94 mg, 74%). HRMS (ESI+) $[M+H]^{+}$ calcd. for $C_{12}H_{16}FN$: 194.1345; found 194.1355. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 12.2$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 2.8$ Hz, H(3_{ax}) + H(5_{ax})], 1.51-1.68 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.21 [1H, br s, NH], 2.45-2.61 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.06 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq} = 12.2$ Hz, H(2_{eq}) + H(6_{eq})], 6.91-6.99 [2H, m, H(3') + H(5')], 7.05-7.12 [2H, m, H(2') + H(6')].

Synthesis method b. Using General Method 4, **48j** (224 mg, 0.76 mmol) and trifluoroacetic acid (2 mL) were reacted in dichloromethane (8 mL) to give **31j** as a clear oil (139 mg, 94%). Data as above.

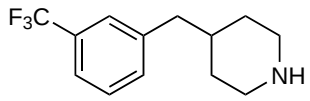
4-(2-Trifluoromethylbenzyl)piperidine (31n)



Using General Method 4, **48n** (311 mg, 0.91 mmol) and trifluoroacetic acid (3 mL) were reacted in dichloromethane (12 mL) to give **31n** as an orange oil (220 mg, 100%). HRMS (ESI+) $[M+H]^{+}$ calcd. for $C_{13}H_{16}F_3N$: 244.1313; found 244.1317. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.59 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 12.9$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 3.1$ Hz, H(3_{ax}) + H(5_{ax})], 1.75-1.89 [3H, m, H(4_{ax}) + H(3_{eq}) + H(5_{eq})], 2.73-2.83 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.35 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq} = 12.9$ Hz, H(2_{eq}) + H(6_{eq})], 7.26 [1H, d, $^{3}J_{5',6'} = 7.6$ Hz, H(6')], 7.33 [1H, t, $^{3}J_{3',4'} = {}^{3}J_{4',5'} = 7.6$ Hz, H(4')],

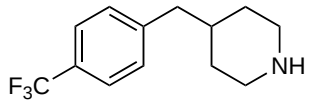
7.47 [1H, t, $^{3}J_{4',5'} = {}^{3}J_{5',6'} = 7.6$ Hz, H(5')], 7.65 [1H, d, $^{3}J_{3',4'} = 7.6$ Hz, H(3')], 7.78 [1H, br s, NH]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 29.12 [C(3) + C(5)], 35.97 [C(4)], 39.03 [C(A)], 44.26 [C(2) + C(6)], 124.54 [q, $^{1}J_{C,F} = 271.9$ Hz, CF_3], 126.43 [q, $^{3}J_{C,F} = 5.7$ Hz, C(3')], 126.63 [C(5')], 128.89 [q, $^{2}J_{C,F} = 29.6$ Hz, C(2')], 131.84 [C(6')], 137.66 [q, $^{4}J_{C,F} = 1.4$ Hz, C(4')], 162.58 [q, $^{3}J_{C,F} = 34.8$ Hz, C(1')].

4-(3-Trifluorobenzyl)piperidine (31o)



Using General Method 4, **48o** (224 mg, 0.65 mmol) and trifluoroacetic acid (2 mL) were reacted in dichloromethane (8 mL) to give **31o** as a yellow oil (159 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{13}H_{16}F_3N$: 244.1313; found 244.1308. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 12.6$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 3.6$ Hz, H(3_{ax}) + H(5_{ax})], 1.69-1.85 [3H, m, H(4_{ax}) + H(3_{eq}) + H(5_{eq})], 2.64 [2H, d, $^{3}J_{4ax,A} = 6.8$ Hz, H(A)], 2.75 [2H, td, $^{2}J_{(2/6)ax,(2/6)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = 12.6$ Hz, $^{3}J_{(2/6)ax,(3/5)eq} = 1.9$ Hz, H(2_{ax}) + H(6_{ax})], 3.30 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq} = 12.6$ Hz, H(2_{eq}) + H(6_{eq})], 7.17-7.36 [2H, m, NH + H(6')], 7.36-7.45 [2H, m, H(2') + H(5')], 7.48 [1H, br d‡, $^{3}J_{4',5'} = 7.8$ Hz, H(4')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 33.18 [C(3) + C(5)], 38.12 [C(4)], 43.64 [C(A)], 46.59 [C(2) + C(6)], 122.85 [q, $^{3}J_{C,F} = 3.8$ Hz, C(4')], 124.38 [q, $^{1}J_{C,F} = 272.2$ Hz, CF_3], 125.81 [q, $^{3}J_{C,F} = 3.8$ Hz, C(2')], 128.66 [C(5')], 130.61 [q, $^{2}J_{C,F} = 31.8$ Hz, C(3')], 132.66 [q, $^{5}J_{C,F} = 1.0$ Hz, C(6')], 141.48 [C(1')].

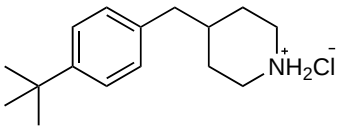
4-(4-Trifluoromethylbenzyl)piperidine (31p)



Synthesis method a. Using General Method 4, **48p** (210 mg, 0.61 mmol) and trifluoroacetic acid (2 mL) were reacted in dichloromethane (8 mL) to give **31p** as a yellow oil (143 mg, 96%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{13}H_{16}F_3N$: 244.1313; found 244.1326. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 13.0$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 3.4$ Hz, H(3_{ax}) + H(5_{ax})], 1.74-1.85 [3H, m, H(4_{ax}) + H(3_{eq}) + H(5_{eq})], 2.66 [2H, d, $^{3}J_{4ax,A} = 6.7$ Hz, H(A)], 2.80 [2H, td, $^{2}J_{(2/6)ax,(2/6)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = 13.0$ Hz, $^{3}J_{(2/6)ax,(3/5)eq} = 2.9$ Hz, H(2_{ax}) + H(6_{ax})], 3.36 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq} = 13.0$ Hz, H(2_{eq}) + H(6_{eq})], 7.21-7.28 [2H, m, H(2') + H(6')], 7.52-7.59 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.73 [C(3) + C(5)], 36.13 [C(4)], 42.21 [C(A)], 44.05 [C(2) + C(6)], 124.18 [q, $^{1}J_{C,F} = 271.9$ Hz, CF_3], 125.47 [q, $^{3}J_{C,F} = 3.8$ Hz, C(3') + C(5')], 128.89 [q, $^{2}J_{C,F} = 32.5$ Hz, C(4')], 129.31 [C(2') + C(6')], 143.06 [C(1')].

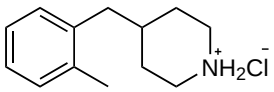
Synthesis method b. Using General Method 6, **49p** (200 mg, 0.71 mmol) and saturated aqueous sodium bicarbonate solution (10 mL) were reacted in dichloromethane (10 mL) to give **31p** as a yellow oil (150 mg, 86%). Data as above.

4-(4-*tert*-Butylbenzyl)piperidine hydrochloride (49a)



Using General Method 5, **36a** (0.50 g, 1.8 mmol), *N*-Boc-4-piperidone (0.18 g, 0.90 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.28 g, 7.0 mmol) were reacted for 18 hr in THF (5 mL), then with Pd-C in methanol (20 mL) for 2 hr followed by hydrogen chloride solution (1M in diethyl ether, 1.5 mL) in diethyl ether (3 mL), to give **49a** as a pale brown solid (0.11 g, 45%). ^{1}H NMR (500 MHz, D_2O): δ 1.19 [9H, s, ^{t}Bu], 1.32 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 13.0$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 3.9$ Hz, H(3_{ax}) + H(5_{ax})], 1.73-1.84 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.50 [2H, d, $^{3}J_{4ax,A} = 6.9$ Hz, H(A)], 2.83 [2H, td, $^{2}J_{(2/6)ax,(2/6)eq} = {}^{3}J_{(2/5)ax,(3/6)ax} = 13.0$ Hz, $^{3}J_{(2/6)ax,(3/5)eq} = 2.8$ Hz, H(2_{ax}) + H(6_{ax})], 3.29 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq} = 13.0$ Hz, H(2_{eq}) + H(6_{eq})], 7.10-7.16 [2H, m, H(3') + H(5')], 7.32-7.39 [2H, m, H(2') + H(6')]. ^{13}C NMR (126 MHz, D_2O): δ 30.70 [C(3) + C(5)], 33.15 [^{t}Bu], 36.36 [^{t}Bu], 37.61 [C(4)], 43.42 [C(A)], 46.60 [C(2) + C(6)], 127.99 [C(3') + C(5')], 131.75 [C(2') + C(6')], 139.65 [C(1')], 152.28 [C(4')].

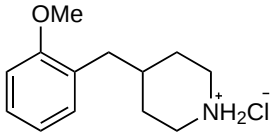
4-(2-Methylbenzyl)piperidine hydrochloride (49b)



Using General Method 5, **36b** (0.50 g, 2.1 mmol), *N*-Boc-4-piperidone (0.21 g, 1.1 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.34 g, 8.5 mmol) were reacted for 18 hr in THF (5 mL), then with Pd-C in methanol (20 mL) for 2 hr followed by hydrogen chloride solution (1M in diethyl ether, 1.5 mL) in diethyl ether (3 mL), to give **49b** as a pale brown solid (0.12 g, 52%). ^{1}H NMR (500 MHz, D_2O): δ 1.38 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 13.0$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 3.9$ Hz, H(3_{ax}) + H(5_{ax})], 1.71-1.85 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.21 [3H, s, CH_3], 2.55 [2H, d, $^{3}J_{4ax,A} = 6.9$ Hz, H(A)], 2.82 [2H, td, $^{2}J_{(2/6)ax,(2/6)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = 13.0$ Hz, $^{3}J_{(2/6)ax,(3/5)eq} = 2.8$ Hz, H(2_{ax}) + H(6_{ax})], 3.30 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq} = 13.0$ Hz, H(2_{eq}) + H(6_{eq})], 7.06-7.21 [4H, m, H(3) + H(4) + H(5) + H(6)]. ^{13}C NMR (126 MHz, D_2O): δ 21.06 [CH_3], 30.90 [C(3) + C(5)], 36.57 [C(4)], 41.27 [C(A)], 46.67 [C(2) + C(6)], 128.42 [C(5')], 129.13 [C(4')], 132.82 [C(6')], 132.91 [C(3')], 139.51 [C(2')], 140.78 [C(1')].

This data is consistent with that reported previously.[123]

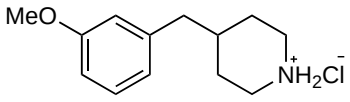
4-(2-Methoxybenzyl)piperidine hydrochloride (49e)



Using General Method 5, **36e** (0.50 g, 1.9 mmol), *N*-Boc-4-piperidone (0.19 g, 0.95 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.31 g, 7.8 mmol) were reacted for 18 hr in THF (5 mL), then with Pd-C in methanol (20 mL) for 2 hr followed by hydrogen chloride solution (1M in diethyl ether, 1.5 mL) in diethyl ether (3 mL), to give **49e** as a pale brown solid (0.12 g, 53%). ^{1}H NMR (500 MHz, D_2O): δ 1.34 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 12.8$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 4.1$ Hz, H(3_{ax}) + H(5_{ax})], 1.69-1.87 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.52 [2H, d, $^{3}J_{4ax,A} = 7.2$ Hz, H(A)], 2.81 [2H, td, $^{2}J_{(2/6)ax,(2/6)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = 12.8$ Hz, $^{3}J_{(2/6)ax,(3/5)eq} = 2.4$ Hz, H(2_{ax}) + H(6_{ax})], 3.28 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq} = 12.8$ Hz, H(2_{eq}) + H(6_{eq})], 3.74 [3H, s, OCH_3], 6.89 [1H, td, $^{3}J_{4',5'} = {}^{3}J_{5',6'} = 7.5$ Hz, $^{4}J_{3',5'} = 1.0$ Hz, H(5')], 6.97 [1H, dd, $^{3}J_{3',4'} = 7.5$ Hz, $^{4}J_{3',5'} = 1.0$ Hz, H(3')], 7.12 [1H, dd, $^{3}J_{5',6'} = 7.5$ Hz, $^{4}J_{4',6'} = 1.7$ Hz, H(6')], 7.20 [1H, td, $^{3}J_{3',4'} = {}^{3}J_{4',5'} = 7.5$ Hz, $^{4}J_{4',6'} = 1.7$ Hz, H(4')]. ^{13}C NMR (126 MHz, D_2O): δ 30.83 [C(3) + C(5)], 36.31 [C(4)], 38.26 [C(A)], 46.66 [C(2) + C(6)], 58.20 [OCH_3], 114.25 [C(3')], 123.47 [C(5')], 130.54 [C(4')], 130.68 [C(1')], 133.79 [C(6')], 159.94 [C(2')].

This data is consistent with that reported previously.[123]

4-(3-Methoxybenzyl)piperidine hydrochloride (49f)

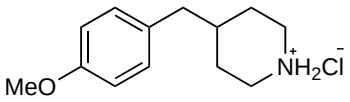


Using General Method 5, **36f** (0.50 g, 1.9 mmol), *N*-Boc-4-piperidone (0.19 g, 0.95 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.31 g, 7.8 mmol) were reacted for 18 hr in THF (5 mL), then with Pd-C in methanol (20 mL) for 2 hr followed by hydrogen chloride solution (1M in diethyl ether, 1.5 mL) in diethyl ether (3 mL), to give **49f** as a pale brown solid (0.14 g, 59%). ^{1}H NMR (500 MHz, D_2O): δ 1.32 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax} = 12.9$ Hz, $^{3}J_{(2/6)eq,(3/5)ax} = 4.0$ Hz, H(3_{ax}) + H(5_{ax})], 1.71-1.86 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.51 [2H, d, $^{3}J_{4ax,A} = 7.1$ Hz, H(A)], 2.82 [2H, td, $^{2}J_{(2/6)ax,(2/6)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = 12.9$ Hz, $^{3}J_{(2/6)ax,(3/5)eq} = 2.6$ Hz, H(2_{ax}) + H(6_{ax})], 3.29 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq} = 12.9$ Hz, H(2_{eq}) + H(6_{eq})], 3.72 [3H, s, OCH_3], 6.75-6.84 [3H, m, H(2') + H(4') + H(6')], 7.21 [1H, t, $^{3}J_{4',5'} = {}^{3}J_{5',6'} = 7.8$ Hz, H(5')]. ^{13}C NMR (126 MHz, D_2O): δ

30.72 [C(3) + C(5)], 37.57 [C(4)], 43.99 [C(A)], 46.65 [C(2) + C(6)], 57.90 [OCH_3], 114.33 [C(4')], 117.46 [C(2')], 124.77 [C(6')], 132.31 [C(5')], 144.49 [C(1')], 161.50 [C(3')].

This data is consistent with that reported previously.[123]

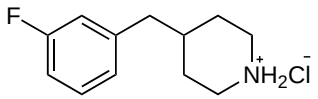
4-(4-Methoxybenzyl)piperidine hydrochloride (49g)



Using General Method 5, **36g** (0.50 g, 1.9 mmol), *N*-Boc-4-piperidone (0.19 g, 0.95 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.31 g, 7.8 mmol) were reacted for 18 hr in THF (5 mL), then with Pd-C in methanol (20 mL) for 2 hr followed by hydrogen chloride solution (1M in diethyl ether, 1.5 mL) in diethyl ether (3 mL), to give **49g** as a yellow solid (0.15 g, 65%). ^{1}H NMR (500 MHz, D_2O): δ 1.30 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax}$ = 13.0 Hz, $^3J_{(2/6)eq,(3/5)ax}$ = 4.3 Hz, H(3_{ax}) + H(5_{ax})], 1.67-1.82 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.47 [2H, d, $^3J_{4ax,A}$ = 6.9 Hz, H(A)], 2.81 [2H, td, $^2J_{(2/6)ax,(2/6)eq} = {}^3J_{(2/6)ax,(3/5)ax}$ = 13.0 Hz, $^3J_{(2/6)ax,(3/5)eq}$ = 1.9 Hz, H(2_{ax}) + H(6_{ax})], 3.28 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq}$ = 13.0 Hz, H(2_{eq}) + H(6_{eq})], 3.71 [3H, s, OCH_3], 6.83-6.89 [2H, m, H(3') + H(5')], 7.07-7.14 [2H, m, H(2') + H(6')]. ^{13}C NMR (126 MHz, D_2O): δ 30.65 [C(3) + C(5)], 37.73 [C(4)], 43.04 [C(A)], 46.64 [C(2) + C(6)], 57.98 [OCH_3], 116.50 [C(3') + C(5')], 132.96 [C(2') + C(6')], 135.15 [C(1')], 159.75 [C(4')].

This data is consistent with that reported previously.[58]

4-(3-Fluorobenzyl)piperidine hydrochloride (49i)

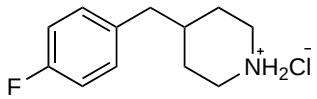


Using General Method 5, **36i** (0.50 g, 2.0 mmol), *N*-Boc-4-piperidone (0.20 g, 1.0 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.32 g, 8.0 mmol) were reacted for 18 hr in THF (5 mL), then with Pd-C in methanol (20 mL) for 2 hr followed by hydrogen chloride solution (1M in diethyl ether, 1.5 mL) in diethyl ether (3 mL), to give **49i** as a yellow solid (0.12 g, 52%). ^{1}H NMR (500 MHz, D_2O): δ 1.32 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax}$ = 12.8 Hz, $^3J_{(2/6)eq,(3/5)ax}$ = 4.0 Hz, H(3_{ax}) + H(5_{ax})], 1.70-1.89 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.54 [2H, d, $^3J_{4ax,A}$ = 7.1 Hz, H(A)], 2.83 [2H, td, $^2J_{(2/6)ax,(2/6)eq} = {}^3J_{(2/6)ax,(3/5)ax}$ = 12.8 Hz, $^3J_{(2/6)ax,(3/5)eq}$ = 2.8 Hz, H(2_{ax}) + H(6_{ax})], 3.29 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq}$ = 12.8 Hz, H(2_{eq}) + H(6_{eq})], 6.87-6.95 [2H, m, H(2') + H(4')], 6.97 [1H, d, $^3J_{5',6'}$ = 7.5 Hz, H(6')], 7.25 [1H, dt, $^3J_{4',5'} = {}^3J_{5',6'}$ = 7.5 Hz, $^3J_{H,F}$ = 5.7 Hz, H(5')]. ^{13}C NMR (126 MHz, D_2O): δ 30.62 [C(3) + C(5)], 37.46 [C(4)], 43.67 [C(A)], 46.60 [C(2)

+ C(6)], 115.47 [d, $^{2}J_{C,F}$ = 21.0 Hz, C(4')], 118.33 [d, $^{2}J_{C,F}$ = 21.0 Hz, C(2')], 127.62 [d, $^{4}J_{C,F}$ = 2.9 Hz, C(6')], 132.57 [d, $^{3}J_{C,F}$ = 8.6 Hz, C(5')], 145.08 [d, $^{3}J_{C,F}$ = 7.6 Hz, C(1')], 165.21 [d, $^{1}J_{C,F}$ = 242.7 Hz, C(3')].

This data is consistent with that reported previously.[58]

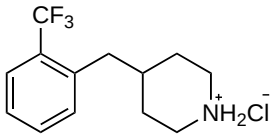
4-(4-Fluorobenzyl)piperidine hydrochloride (49j)



Using General Method 5, **36j** (0.50 g, 2.0 mmol), *N*-Boc-4-piperidone (0.20 g, 1.0 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.32 g, 8.0 mmol) were reacted for 18 hr in THF (5 mL), then with Pd-C in methanol (20 mL) for 2 hr followed by hydrogen chloride solution (1M in diethyl ether, 1.5 mL) in diethyl ether (3 mL), to give **49j** as a brown solid (0.17 g, 74%). ^{1}H NMR (500 MHz, D_2O): δ 1.30 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq}$ = $^{3}J_{(2/6)ax,(3/5)ax}$ = $^{3}J_{(3/5)ax,4ax}$ = 12.9 Hz, $^{3}J_{(2/6)eq,(3/5)ax}$ = 3.9 Hz, H(3_{ax}) + H(5_{ax})], 1.69-1.84 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.50 [2H, d, $^{3}J_{4ax,A}$ = 6.9 Hz, H(A)], 2.82 [2H, td, $^{2}J_{(2/6)ax,(2/6)eq}$ = $^{3}J_{(2/6)ax,(3/5)ax}$ = 12.9 Hz, $^{3}J_{(2/6)ax,(3/5)eq}$ = 2.2 Hz, H(2_{ax}) + H(6_{ax})], 3.28 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq}$ = 12.9 Hz, H(2_{eq}) + H(6_{eq})], 6.94-7.01 [2H, m, H(3') + H(5')], 7.10-7.17 [2H, m, H(2') + H(6')]. ^{13}C NMR (126 MHz, D_2O): δ 30.60 [C(3) + C(5)], 37.68 [C(4)], 43.12 [C(A)], 46.62 [C(2) + C(6)], 117.52 [d, $^{2}J_{C,F}$ = 21.5 Hz, C(3') + C(5')], 133.26 [d, $^{3}J_{C,F}$ = 8.1 Hz, C(2') + C(6')], 138.16 [d, $^{4}J_{C,F}$ = 2.9 Hz, C(1')], 163.80 [d, $^{1}J_{C,F}$ = 241.3 Hz, C(4')].

This data is consistent with that reported previously.[58]

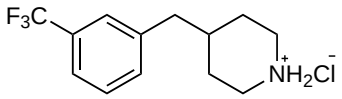
4-(2-Trifluoromethylbenzyl)piperidine hydrochloride (49n)



Using General Method 5, **36n** (0.50 g, 1.7 mmol), *N*-Boc-4-piperidone (0.19 g, 0.95 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.32 g, 8.0 mmol) were reacted for 18 hr in THF (5 mL), then with Pd-C catalyst in methanol (20 mL) for 2 hr followed by hydrogen chloride solution (1M in diethyl ether, 1.5 mL) in diethyl ether (3 mL), to give **49n** as a brown solid (72 mg, 27%). ^{1}H NMR (500 MHz, D_2O): δ 1.52 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq}$ = $^{3}J_{(2/6)ax,(3/5)ax}$ = $^{3}J_{(3/5)ax,4ax}$ = 13.0 Hz, $^{3}J_{(2/6)eq,(3/5)ax}$ = 4.0 Hz, H(3_{ax}) + H(5_{ax})], 1.85-1.95 [2H, m, H(3_{eq}) + H(5_{eq})], 1.95-2.08 [1H, m, H(4_{ax})], 2.84 [2H, d, $^{3}J_{4ax,A}$ = 7.2 Hz, H(A)], 2.95 [2H, td, $^{2}J_{(2/6)ax,(2/6)eq}$ = $^{3}J_{(2/6)ax,(3/5)ax}$ = 13.0 Hz, $^{3}J_{(2/6)ax,(3/5)eq}$ = 2.8 Hz, H(2_{ax}) +

$H(6_{ax})$], 3.43 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq}$ = 13.0 Hz, $H(2_{eq})$ + $H(6_{eq})$], 7.45 [1H, t, $^{3}J_{3',4'}$ = $^{3}J_{4',5'}$ = 7.7 Hz, H(4')], 7.48 [1H, d, $^{3}J_{5',6'}$ = 7.7 Hz, H(6')], 7.61 [1H, t, $^{3}J_{4',5'}$ = $^{3}J_{5',6'}$ = 7.7 Hz, H(5')], 7.77 [1H, d, $^{3}J_{3',4'}$ = 7.7 Hz, H(3')]. ^{13}C NMR (126 MHz, D_2O): δ 30.83 [C(3) + C(5)], 37.48 [C(4)], 40.51 [C(A)], 46.69 [C(2) + C(6)], 127.25 [q, $^{1}J_{C,F}$ = 273.0 Hz, CF_3], 128.77 [q, $^{3}J_{C,F}$ = 5.7 Hz, C(3')], 129.21 [C(5')], 130.78 [q, $^{2}J_{C,F}$ = 29.3 Hz, C(2')], 134.46 [C(6')], 134.60 [br‡, C(4')], 140.65 [q, $^{3}J_{C,F}$ = 1.6 Hz, C(1')].

4-(3-Trifluoromethylbenzyl)piperidine hydrochloride (49o)

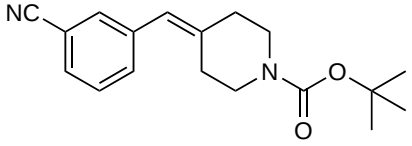


Using General Method 5, **36o** (0.50 g, 1.7 mmol), *N*-Boc-4-piperidone (0.19 g, 0.95 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.31 g, 7.8 mmol) were reacted for 18 hr in THF (5 mL), then with Pd-C in methanol (20 mL) for 2 hr followed by hydrogen chloride solution (1M in diethyl ether, 1.5 mL) in diethyl ether (3 mL), to give **49o** as a pale yellow solid (158 mg, 59%). ^{1}H NMR (500 MHz, D_2O): δ 1.30 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq}$ = $^{3}J_{(2/6)ax,(3/5)ax}$ = $^{3}J_{(3/5)ax,4ax}$ = 13.0 Hz, $^{3}J_{(2/6)eq,(3/5)ax}$ = 4.2 Hz, $H(3_{ax})$ + $H(5_{ax})$], 1.65-1.85 [3H, m, $H(3_{eq})$ + $H(4_{ax})$ + $H(5_{eq})$], 2.56 [2H, d, $^{3}J_{4ax,A}$ = 7.2 Hz, H(A)], 2.78 [2H, td, $^{2}J_{(2/6)ax,(2/6)eq}$ = $^{3}J_{(2/6)ax,(3/5)ax}$ = 13.0 Hz, $^{3}J_{(2/6)ax,(3/5)eq}$ = 2.8 Hz, $H(2_{ax})$ + $H(6_{ax})$], 3.25 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq}$ = 13.0 Hz, $H(2_{eq})$ + $H(6_{eq})$], 7.32-7.40 [2H, m, H(5') + H(6')], 7.40-7.48 [2H, m, H(2') + H(4')]. ^{13}C NMR (126 MHz, D_2O): δ 30.61 [C(3) + C(5)], 37.53 [C(4)], 43.70 [C(A)], 46.61 [C(2) + C(6)], 125.62 [q, $^{3}J_{C,F}$ = 3.9 Hz, C(4')], 128.27 [q, $^{3}J_{C,F}$ = 3.8 Hz, C(2')], 131.60 [C(5')], 132.52 [q, $^{2}J_{C,F}$ = 31.6 Hz, C(3')], 135.53 [C(6')], 143.35 [C(1')].

This data is consistent with that reported previously.[58]

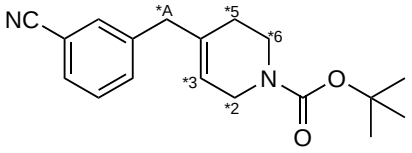
6.2.2 Investigation of 4-benzylpiperidine synthesis

***tert*-Butyl 4-(3-cyanobenzylidene)piperidine-1-carboxylate (45r)**



Synthesis method a. Using General Method 2, **36r** (0.50 g, 2.0 mmol), *N*-Boc-4-piperidone (0.22 g, 1.1 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.30 g,7.5 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography

on silica gel eluting with 1:9 ethyl acetate/hexane to give a mixture of **45r** and *tert*-butyl 4-(3-cyanobenzyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (**55r**) as a colourless oil which could not be purified (122 mg, 37%). ^{1}H NMR analysis indicated the mixture after column chromatography contained approximately a 2:3 ratio of **45r** and **55r**.



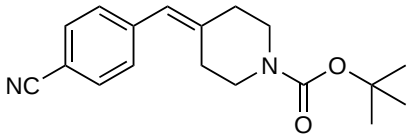
55r

tert-*butyl 4-(3-cyanobenzyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (**55r**) and* tert-*Butyl 4-(3-cyanobenzylidene)piperidine-1-carboxylate (**45r**):* R_f = 0.13 (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{23}NO_2 - C(CH_3)_3$: 243.1134; found 243.1140. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42-1.51 [9H, s, ^{t}Bu + *^{t}Bu], 1.97 [1.2H, br s‡, *H(5)], 2.31-2.38 [1.6H, H(3) + H(5)], 3.34 [1.2H, br s, *H(A)], 3.37-3.57 [2.8H, m, H(2) + H(6) + *H(6)], 3.90 [1.2H, br s‡, *H(2)], 5.40 [0.6H, br s‡, *H(3)], 6.32 [0.4H, s, H(A)], 7.32-7.60 [4H, m, Ar H + *Ar H].

Synthesis method b. A solution of LiHMDS (1M in THF, 3.0 mL, 3.0 mmol) was added to a stirring solution of **36r** (750 mg, 3.0 mmol) in anhydrous THF (5 mL) under an atmosphere of nitrogen. The reaction mixture was stirred for 15 minutes and a solution of *N*-Boc-4-piperidone (320 mg, 1.60 mmol) in THF (2 mL) was added dropwise. The mixture was stirred for 16 hr then the reaction was quenched with water and extracted with ethyl acetate (3 x 40 mL), with the organic extracts dried over $MgSO_4$ and filtered. Volatile solvent was removed by evaporation under reduced pressure and the residue purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45r** as a white solid (258 mg, 54%). R_f = 0.13 (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{23}NO_2 - C(CH_3)_3$: 243.1134; found 243.1140. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.29-2.46 [4H, m, H(3) + H(5)], 3.36-3.46 [2H, m, H(2)], 3.48-3.58 [2H, m, H(6)], 6.32 [1H, s, H(A)], 7.37-7.53 [4H, m, H(2') + H(4') + H(5') + H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.58 [^{t}Bu], 29.32 [br, C(3)], 36.29 [br, C(5)], 45.29 [br, C(2) + C(6)], 79.90 [^{t}Bu], 112.57 [C(3')], 118.98 [CN], 122.61 [C(A)], 129.17 [C(5')], 130.00 [C(2')], 132.46 [C(4')], 133.40 [C(6')], 138.75 [C(1')], 141.35 [C(4)], 154.81 [C=O].

^{1}H NMR data for this compound has been reported previously,[124] but was not consistent with data reported here.

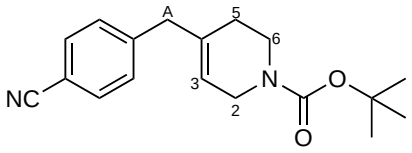
tert-Butyl 4-(4-cyanobenzylidene)piperidine-1-carboxylate (45s)



Synthesis method a. Using General Method 2, **36s** (0.56 g, 2.2 mmol), *N*-Boc-4-piperidone (0.22 g, 1.1 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.18 g, 4.4 mmol) were reacted in THF (5 mL) for 18 hr. Separation of the crude mixture* was attempted using repeated flash column chromatography on silica gel eluting with 6% ethyl acetate in hexane, which yielded a sample of pure **45s** as a white solid (22 mg, 7%), and a sample of *tert*-butyl 4-(4-cyanobenzyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (**55s**) as a clear oil (44 mg, 13%). The remaining mixture of co-eluted products was also collected but could not be purified.

*Note: ^{1}H NMR analysis of the crude mixture before column chromatography indicated a product ratio of 1:3.7 **45s**/**55s**.

tert-*Butyl 4-(4-cyanobenzylidene)piperidine-1-carboxylate (**45s**):* R_f = 0.33 (1:4 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{22}N_2O_2 - C(CH_3)_3$: 243.1134; found 243.1128. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.30-2.40 [2H, m, H(5)], 2.40-2.51 [2H, m, H(3)], 3.36-3.46 [2H, m, H(2)], 3.48-3.59 [2H, m, H(6)], 6.36 [1H, s, H(A)], 7.25-7.32 [2H, m, H(2') + H(6')], 7.57-7.63 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.44 [^{t}Bu], 29.32 [br, C(3)], 36.30 [br, C(5)], 44.71 [br, C(2) + C(6)], 79.77 [^{t}Bu], 109.83 [C(4')], 118.99 [CN], 123.23 [C(A)], 129.49 [C(2') + C(6')], 132.01 [C(3') + C(5')], 141.89 [C(4)], 142.20 [C(1')], 154.65 [C=O].



55s

tert-*Butyl 4-(4-cyanobenzyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (**55s**):* R_f = 0.26 (1:4 ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 [9H, s, ^{t}Bu], 1.96 [2H, br s‡, H(5)], 3.37 [2H, br s, H(A)], 3.42-3.51 [2H, m, H(6)], 3.89 [2H, br s‡, H(2)], 5.41 [1H, br s‡, H(3)], 7.25-7.31 [2H, m, H(2') + H(6')], 7.56-7.63 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.22 [br, C(5)], 28.56 [^{t}Bu], 39.75 [br, C(6)], 43.51 [br, C(2)], 43.85 [C(A)], 79.74 [^{t}Bu], 110.35 [C(4')], 119.05 [CN], 121.03 [br, C(3)], 129.85 [C(2') + C(6')], 132.31 [C(3') + C(5')], 134.84 [br, C(4)], 144.95 [C(1')], 154.97 [C=O].

This data is consistent with that reported previously.[70]

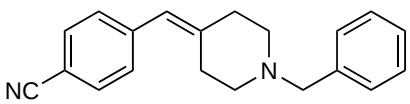
Synthesis method b. A solution of LiHMDS (1M in THF, 4.0 mL, 4.0 mmol) was added to a stirring solution of **36s** (1.00 g, 4.0 mmol) in anhydrous THF (6 mL) under an atmosphere of nitrogen. The reaction mixture was stirred for 15 minutes and a solution of *N*-Boc-4-piperidone (400 mg, 2.0 mmol) in THF (2 mL) was added dropwise. The mixture was stirred for 16 hr then quenched with water and extracted with ethyl acetate (3 x 40 mL), and the organic extracts were dried over $MgSO_4$ and filtered. Volatile solvent was removed by evaporation under reduced pressure and the residue purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45s** as a white solid (593 mg, 99%). $R_f = 0.40$ (1:4 ethyl acetate/hexane). Data as above.

Synthesis method c. A sample of pure **45s** (25 mg, 0.08 mmol) was stirred in THF (3 mL) with sodium hydride (60% in mineral oil, 50 mg, 1.25 mmol) at 30°C for 16 hr. The mixture was quenched with water, and extracted with ethyl acetate (3 x 25 mL). Volatile solvent was removed by evaporation under reduced pressure, and the residue was chromatographed over silica gel with 5% ethyl acetate/hexane as eluant to give a mixture of **45s** and **55s** as a colourless oil (15 mg, 60%). ^{1}H NMR analysis of the mixture determined a product ratio of 1:3.8 **45s**/**55s**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39-1.51 [9H, m, ^{t}Bu + *^{t}Bu], 1.96 [1.6H, br s‡, *H(5)], 2.32-2.41 [0.4H, m, H(5)], 2.40-2.48 [0.4H, m, H(3)], 3.36 [1.6H, br s, *H(A)], 3.38-3.50 [2H, m, H(2) + *H(6)], 3.50-3.56 [0.4H, m, H(6)], 3.89 [1.6H, br s‡, *H(2)], 5.41 [0.8H, br s‡, *H(3)], 6.36 [0.2H, s, H(A)], 7.22-7.33 [2H, m, H(2') + H(6') + *H(2') + *H(6')], 7.54-7.63 [2H, m, H(3') + H(5') + *H(3') + *H(5')].

* denotes signals corresponding to side-product **55s**.

Synthesis method d. A sample of pure **55s** (25 mg, 0.08 mmol) was stirred in THF (3 mL) with sodium hydride (60% in mineral oil, 50 mg, 1.25 mmol) at 30°C overnight. The mixture was quenched with water, and extracted with ethyl acetate (3 x 25 mL). Volatile solvent was removed by evaporation under reduced pressure, and the residue was chromatographed over silica gel with 1:19 ethyl acetate/hexane as eluant to give a mixture of **45s** and **45s** as a colourless oil (17 mg, 68%). ^{1}H NMR analysis of the mixture determined a product ratio of 1:3.8 **45s**/**55s**. Data as above.

4-((1-Benzylpiperidin-4-ylidene)methyl)benzonitrile (47s)

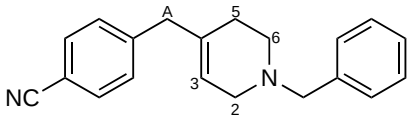


Using General Method 2, **36s** (0.67 g, 2.6 mmol), *N*-Bn-4-piperidone **46** (0.25 g, 1.3 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.21 g, 5.3 mmol) were reacted in THF (5 mL) for 4 hr. The crude product was purified by column chromatography on silica gel eluting with 1:1 ethyl acetate/hexane to give **47s** as a white powder (301 mg, 81%) and

4-((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methyl)benzonitrile (**56s**) as a clear oil (38 mg, 10%).

*4-((1-Benzylpiperidin-4-ylidene)methyl)benzonitrile (**47s**):* R_f = 0.50 (1:1 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{20}H_{20}N_2$: 289.1705; found 289.1701. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.37-2.46 [4H, m, H(3) + H(5)], 2.46-2.58 [4H, m, H(2) + H(6)], 3.52 [2H, s, CH_2], 6.25 [1H, s, H(A)], 7.21-7.36 [7H, m, H(2') + H(6') + Ph], 7.53-7.60 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 29.41 [C(3)], 36.73 [C(5)], 54.25 [*C(2) or C(6)], 54.91 [*C(2) or C(6)], 62.94 [CH_2], 109.57 [C(4')], 119.21 [CN], 121.97 [C(A)], 127.15 [C(4'')], 128.31 [C(3'') + C(5'')], 129.18 [C(2'') + C(6'')], 129.60 [C(2') + C(6')], 132.00 [C(3') + C(5')], 138.36 [C(1'')], 142.76 [C(1')], 143.44 [C(4)].

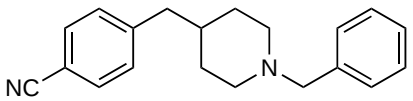
*Interpretation of spectra and 2D NMR correlations could not achieve unambiguous assignment of all NMR signals due to overlapped signals in the ^{1}H NMR spectrum.



56s

*4-((1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl)methyl)benzonitrile (**56s**):* R_f = 0.23 (1:1 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{20}H_{20}N_2$: 289.1705; found 289.1712. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.98-2.04 [2H, m, H(5)], 2.54 [2H, t, $^3J_{5,6}$ = 5.8 Hz, H(6)], 2.99 [2H, br s‡, H(2)], 3.33 [2H, br s, H(A)], 3.57 [2H, s, CH_2], 5.38 [1H, br s‡, H(3)], 7.22-7.35 [7H, m, H(2') + H(6') + Ph], 7.55-7.60 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 29.10 [C(5)], 43.65 [C(A)], 49.80 [C(6)], 52.87 [C(2)], 62.77 [CH_2], 110.18 [C(4')], 119.20 [CN], 122.25 [C(3)], 127.25 [C(4'')], 128.37 [C(3'') + C(5'')], 129.35 [C(2'') + C(6'')], 129.96 [C(2') + C(6')], 132.26 [C(3') + C(5')], 134.71 [C(4)], 138.15 [C(1'')], 145.42 [C(1')].

4-((1-Benzylpiperidin-4-yl)methyl)benzonitrile (57s)



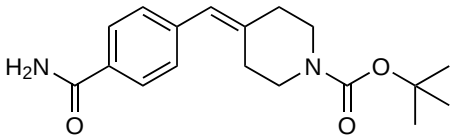
Synthesis method a. Using General Method 3, **47s** (288 mg, 1.00 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr to give **57s** as a clear oil, which was used without further purification (187 mg, 64%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{20}H_{22}N_2$: 291.1861; found 291.1864. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax}$ = 11.7 Hz, $^3J_{(2/6)eq,(3/5)ax}$ = 3.5 Hz, H(3_{ax}) + H(5_{ax})], 1.47-1.60 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 1.90 [2H, br t‡, $^2J_{(2/6)ax,(2/6)eq}$ =

$^{3}J_{(2/6)ax,(3/5)ax}$ = 11.7 Hz, H(2_{ax}) + H(6_{ax})], 2.58 [2H, d, $^{3}J_{4ax,A}$ = 6.7 Hz, H(A)], 2.86 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq}$ = 11.7 Hz, H(2_{eq}) + H(6_{eq})], 3.47 [2H, s, CH_2], 7.18-7.40 [7H, m, H(2') + H(6') + Ph], 7.51-7.59 [2H, m, H(3') + H(5')].

Synthesis method b. Using General Method 3, **56s** (20 mg, 0.07 mmol) was reacted with Pd-C catalyst in methanol (20 mL) under a hydrogen atmosphere for 2 hr to give an impure mixture containing **57s** and **56s** (3:2 ratio, determined by ^{1}H NMR analysis).

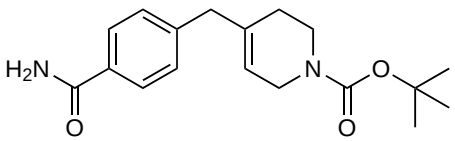
Synthesis method c. Using General Method 3, **56s** (20 mg, 0.07 mmol) was reacted with Pd-C catalyst in methanol (20 mL) under a hydrogen atmosphere for 16 hr to give **57s** as a clear oil, which was used without further purification (17 mg, 84%). Data as above.

tert-Butyl 4-(4-carbamoylbenzylidene)piperidine-1-carboxylate (59)



N-Boc-4-piperidone (250 mg, 1.25 mmol) and **36s** (400 mg, 1.58 mmol) were combined in ethanol (4 mL) with water (1 drop). Potassium hydroxide pellets (0.35 g, 6.24 mmol) were added over 10 minutes. The mixture was stirred at room temperature for 30 min then 70°C for 2 hr, before cooling to 60°C and adding ice water (10 mL). The mixture was stirred at 0°C for 30 min and no precipitate was formed. The ethanol was removed by evaporation under reduced pressure and mixture extracted with ethyl acetate. The volatile solvent was removed by evaporation under reduced pressure and the residue was purified by column chromatography on silica gel eluting with 1:4 ethyl acetate/hexane to give an inseparable mixture of **59** and *tert*-butyl 4-(4-carbamoylbenzyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (**60**) as a white solid (264 mg, combined yield 67%). R_f = 0.21 (1:1 ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 [5.4H, s, *^{t}Bu], 1.48 [3.6H, s, ^{t}Bu], 1.98 [1.2H, br s‡, *H(5)], 2.32-2.38 [0.8H, m, H(5)], 2.43-2.49 [0.8H, m, H(3)], 3.36 [1.2H, br s, *H(A)], 3.38-3.48 [2H, m, H(2) + *H(6)], 3.49-3.56 [0.8H, m, H(6)], 3.89 [1.2H, br s‡, *H(2)], 5.40 [0.6H, br s‡, *H(3)], 5.49-6.20 [2H, m, $CONH_2$ + *$CONH_2$], 6.38 [0.4H, s, H(A)], 7.21-7.30 [2H, m, H(2') + H(6') + *H(2') + *H(6')], 7.71-7.80 [2H, m, H(3') + H(5') + *H(3') + *H(5')].

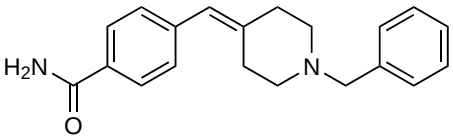
* corresponds to side-product **60**.



60

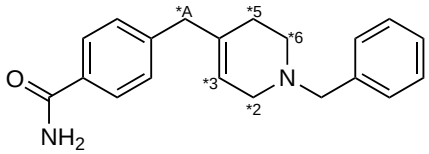
A sample of pure **59** was obtained by repeated recrystallisation from hexane for the purposes of characterisation. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.29-2.40 [2H, m, H(5)], 2.41-2.51 [2H, m, H(3)], 3.36-3.46 [2H, m, H(2)], 3.48-3.57 [2H, m, H(6)], 5.76-6.25 [2H, m, $CONH_2$], 6.38 [1H, s, H(A)], 7.22-7.30 [2H, m, H(2') + H(6')], 7.73-7.82 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.59 [^{t}Bu], 29.44 [C(3)], 36.42 [C(5)], 45.07 [br, C(2) + C(6)], 79.84 [^{t}Bu], 123.84 [C(A)], 127.47 [C(3') + C(5')], 129.18 [C(2') + C(6')], 131.17 [C(4')], 140.64 [C(1')], 141.48 [C(4)], 154.86 [C=O], 169.20 [$CONH_2$].

4-((1-Benzylpiperidin-4-ylidene)methyl)benzamide (58)



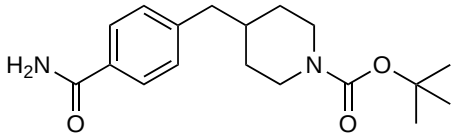
N-Bn-4-piperidone (240 mg, 1.3 mmol) and **36s** (400 mg, 1.58 mmol) were combined in ethanol (4 mL) with water (1 drop). Potassium hydroxide pellets (0.35 g, 6.2 mmol) were added over 10 minutes. The mixture was stirred at room temperature for 30 min then 70°C for 2 hr, before cooling to 60°C and adding ice water (10 mL). The mixture was stirred at 0°C for 30 min and the resulting precipitate collected by vacuum filtration, washing with ice cold water to give an inseparable mixture of **58** and 4-((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methyl)benzamide (**61**) as a white solid (264 mg, combined yield 68%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{20}H_{22}N_2O$: 307.1810; found 307.1807. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.92-2.13 [0.2H, m, *H(5)], 2.37-2.58 [3.4H, m, H(2) + H(3) + H(5) + H(6) + *H(6)], 2.98 [0.2H, br s‡, *H(2)], 3.33 [0.2H, br s, *H(A)], 3.53 [1.8H, s, CH_2], 3.56 [0.2H, s, *CH_2], 5.38 [0.1H, br s‡, *H(3)], 5.69-6.23 [2H, m, $CONH_2$ + *$CONH_2$], 6.28 [0.9H, s, H(A)], 7.20-7.36 [7H, m, H(2') + H(6') + Ph + *H(2') + *H(6') + *Ph], 7.70-7.78 [2H, m, H(3') + H(5') + *H(3') + *H(5')].

* Denotes signals corresponding to the minor product, **61**.



61

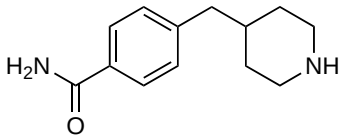
tert-Butyl 4-(4-carbamoylbenzylidene)piperidine-1-carboxylate (64)



Using General Method 3, a mixture of **59** and **60** (254 mg, 0.80 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under an atmosphere of hydrogen for 18 hr to give crude **64** as a clear oil which was used without further purification (241 mg, 94%). $R_f = 0.30$ (1:4 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{26}N_2O_3$: 263.1396; found 263.1390. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax}$ = 12.2 Hz, $^3J_{(3/5)ax,(2/6)eq}$ = 3.7 Hz, H(3_{ax}) + H(5_{ax})], 1.45 [9H, s, ^{t}Bu], 1.54-1.75 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.53-2.73 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 4.07 [2H, br s‡, H(2_{eq}) + H(6_{eq})], 5.78-6.32 [2H, m, $CONH_2$], 7.17-7.26 [2H, m, H(2') + H(6')], 7.70-7.79 [2H, m, H(3') + H(5')].

^{1}H NMR data for this compound has been reported previously,[124] but was not consistent with data reported here.

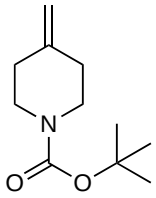
tert-Butyl 4-(4-carbamoylbenzylidene)piperidine-1-carboxylate (65)



Using General Method 4, **64** (230 mg, 0.72 mmol) was reacted with trifluoroacetic acid (2 mL) to give **65** as a clear oil (72 mg, 46%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{13}H_{18}N_2O$: 219.1497; found 219.1494. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax}$ = 12.1 Hz, $^3J_{(2/6)eq,(3/5)ax}$ = 3.5 Hz, H(3_{ax}) + H(5_{ax})], 1.57-1.71 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.10 [1H, br s, NH], 2.51-2.61 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.06 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq}$ = 12.1 Hz, H(2_{eq}) + H(6_{eq})], 5.67-6.29 [2H, m, $CONH_2$], 7.17-7.25 [2H, m, H(2') + H(6')], 7.69-7.76 [2H, m, H(3') + H(5')].

This data is consistent with that reported previously.[75]

tert-Butyl 4-methylenepiperidine-1-carboxylate (66)

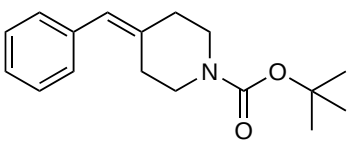


Synthesis method a. Anhydrous THF (4 mL) was added to methyltriphenylphosphonium bromide (0.54 g, 1.5 mmol) under an N_2 atmosphere. The mixture was cooled to -78°C and *n*-BuLi (2M in hexanes, 753 μL, 1.51 mmol) was added dropwise. The mixture was stirred for 30 min then a solution of *N*-Boc-4-piperidone (0.20 g, 1.00 mmol) in THF was added over 5 min. The mixture was warmed to room temperature and stirred for 48 hr then quenched with brine and extracted with ethyl acetate (3 x 30 mL). The organic extracts were dried over $MgSO_4$, filtered, and solvent removed by evaporation under reduced pressure. The residue was re-suspended in 1:1 ethyl acetate/hexane (10 mL) and filtered to remove insoluble by-products, then purified by column chromatography on silica gel eluting with 3:7 ethyl acetate/hexane to give **66** as a pale yellow oil (76 mg, 40%). R_f = 0.72 (1:1 ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 [9H, s, ^{t}Bu], 2.13-2.22 [2H, m, H(3) + H(5)], 3.37-3.46 [2H, m, H(2) + H(6)], 4.74 [2H, s, $=CH_2$].

This data is consistent with that reported in literature previously.[125]

Synthesis method b. Anhydrous THF (6 mL) was added to a mixture of methyltriphenylphosphonium bromide (0.54 g, 1.5 mmol) and sodium hydride (60% in mineral oil, 0.18 g, 4.5 mmol) under an N_2 atmosphere and the mixture was stirred for 30 min. A solution of *N*-Boc-4-piperidone (0.20 g, 1.00 mmol) in THF was added and the mixture stirred for 48 hr then quenched with brine solution (25 mL) and extracted with ethyl acetate (3 x 30 mL). The organic extracts were dried over $MgSO_4$, filtered, and solvent removed by evaporation under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate/hexane (1:1) to give **66** as a pale yellow oil (160 mg, 81%). Data as above.

tert-Butyl 4-benzylidenepiperidine-1-carboxylate (45x)



Synthesis method a. Bromobenzene (100 mg, 0.64 mmol) and **5** (25 mg, 0.13 mmol) were combined with potassium carbonate (53 mg, 0.38 mmol), tri-*o*-tolylphosphine (2.7 mg, 8.9 μmmol) and $Pd(OAc)_2$ (1.4 mg, 6.3 μmmol) in DMF (2 mL) and the mixture

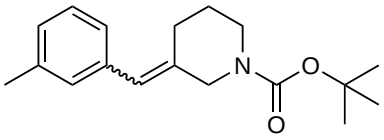
was stirred at 80°C for 48 hours. The mixture was cooled and filtered through Celite® washing with methanol, and the solvent was removed by evaporation under reduced pressure to give an orange residue. ^{1}H NMR analysis of crude mixture indicated the presence of **45x**, but attempted purification by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane did not yield any pure product.

Synthesis method b. Using General Procedure 2, **36x** (0.50 g, 2.2 mmol), *N*-Boc-4-piperidone (0.20 g, 1.0 mmol) and sodium hydride (60% dispersion in paraffin oil, 0.30 g, 7.5 mmol) were reacted in THF (5 mL) for 18 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **45x** as a white solid (135 mg, 49%). R_f = 0.36 (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{23}NO_2 - C(CH_3)_3$: 218.1181; found 218.1171. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.26-2.38 [2H, m, H(5)], 2.41-2.51 [2H, m, H(3)], 3.33-3.44 [2H, m, H(2)], 3.46-3.57 [2H, m, H(6)], 6.36 [1H, s, H(A)], 7.15-7.23 [3H, m, H(2') + H(4') + H(6')], 7.27-7.35 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.59 [^{t}Bu], 29.31 [br, C(3)], 36.34 [br, C(5)], 45.31 [br, C(2) + C(6)], 79.65 [^{t}Bu], 124.64 [C(A)], 126.42 [C(4')], 128.28 [C(2') + C(6')], 128.99 [C(3') + C(5')], 137.56 [C(1')], 138.53 [C(4)], 154.88 [C=O].

This data is consistent with that reported previously.[126]

6.2.3 Synthesis of benzylpiperidine variants

tert-Butyl 3-(3-methylbenzylidene)piperidine-1-carboxylate (67c)

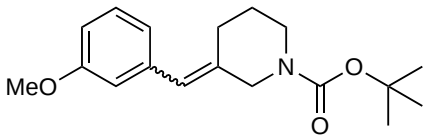


Using General Method 2, **36c** (0.75 g, 3.1 mmol), *N*-Boc-3-piperidone (0.31 g, 1.6 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.40 g, 10.0 mmol) were reacted in THF (5 mL) for 48 hrs. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **67c** as a colourless oil (176 mg, 39%). R_f = 0.30 (1:9 ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 [1.8H, br s, *^{t}Bu], 1.48 [7.2H, s, ^{t}Bu], 1.56-1.65 [1.6H, m, H(5)], 1.67-1.74 [0.4H, m, *H(5)], 2.34 [3H, s, CH_3 + *CH_3], 2.36-2.41 [0.4H, m, *H(4)], 2.48-2.55 [1.6H, m, H(4)], 3.45-3.53 [2H, m, H(6) + *H(6)], 4.00 [1.6H, br s, H(2)], 4.18 [0.4H, br s, *H(2)], 6.30 [0.2H, br s, *H(A)], 6.38 [0.8H, br s, H(A)], 6.97-7.08 [3H, m, H(2') + H(4') + H(6') + *H(2') + *H(4') + *H(6')], 7.17-7.24 [1H, m, H(5') + *H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.56 [CH_3 + *CH_3], 26.13 [br, C(5)], 26.99 [*C(5)], 27.53 [C(4)], 28.35 [br, *^{t}Bu], 28.63 [br, ^{t}Bu], 34.84 [br, *C(4)], 44.51 [br, C(6) + *C(6)], 51.22-53.35 [C(2) + *C(2)], 79.44 [br, *^{t}Bu], 79.60

[br, ^{t}Bu], 125.10 [C(A) + *C(A')], 125.91-126.17 [C(4') + *C(4')], 127.21-127.58 [C(6') + *C(6')], 128.01-128.30 [C(5') + *C(5')], 129.48-129.86 [C(2') + *C(2')], 135.75-136.44 [C(3) +*C(3)], 137.19 [C(3') + *C(3')], 137.70-137.89 [C(1') + *C(1')], 154.81 [*C=O], 154.92 [C=O].

* denotes *Z*-isomer

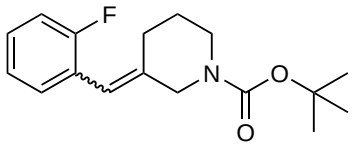
tert-Butyl 3-(3-methoxybenzylidene)piperidine-1-carboxylate (67f)



Using General Method 2, **36f** (0.78 g, 3.0 mmol), *N*-Boc-3-piperidone (0.30 g, 1.5 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.48 g, 12.0 mmol) were reacted in THF (5 mL) for 48 hrs. The crude product was purified by column chromatography on silica gel eluting with 1:19 ethyl acetate/hexane to give **67f** as a colourless oil (96 mg, 21%). R_f = 0.25 (1:9 ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 [2.7H, br s, *^{t}Bu], 1.48 [6.3H, s, ^{t}Bu], 1.57-1.65 [1.4H, m, H(5)], 1.68-1.75 [0.6H, m, *H(5)], 2.36-2.41 [0.6H, m, *H(4)], 2.49-2.55 [1.4H, m, H(4)], 3.46-3.53 [2H, m, H(6) + *H(6)], 3.78-3.83 [3H, m, OCH_3 + *OCH_3], 4.01 [1.4H, br s, H(2)], 4.19 [0.6H, br s, *H(2)], 6.30 [0.3H, br s, *H(A)], 6.39 [0.7H, br s, H(A)], 6.73-6.86 [3H, m, H(2') + H(4') + H(6') + *H(2') + *H(4') + *H(6')], 7.20-7.26 [1H, m, H(5') + *H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 26.10 [br, C(5)], 26.91 [*C(5)], 27.58 [C(4)], 28.36 [br, *^{t}Bu], 28.62 [br, ^{t}Bu], 34.82 [br, *C(4)], 44.59 [br, C(6)], 46.12 [br, *C(6)], 51.62 [br, *C(2)], 52.77 [br, C(2)], 55.30 [OCH_3], 55.32 [*OCH_3], 79.52 [br, *^{t}Bu], 79.64 [br, ^{t}Bu], 112.11 [C(4') + *C(4')], 114.66 [C(2') + *C(2')], 121.41 [*C(6')], 121.52 [C(6')], 124.90 [br, C(A) + *C(A)], 129.24 [br, C(5') + *C(5')], 136.58 [br, C(3) + *C(3)], 138.65 [br, C(1') + *C(1')], 154.76 [*C=O], 154.92 [C=O], 159.52 [C(3')], 159.62 [*C(3')].

* denotes *Z*-isomer

tert-Butyl 3-(2-fluorobenzylidene)piperidine-1-carboxylate (67h)

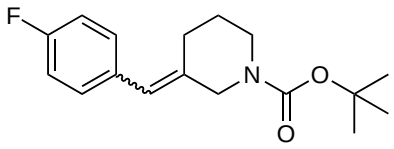


Using General Method 2, **36h** (0.50 g, 2.0 mmol), *N*-Boc-3-piperidone (0.20 g, 1.0 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.31 g, 7.8 mmol) were reacted in THF (5 mL) for 48 hrs. The crude product was purified by column chromatography on silica gel

eluting with 1:9 ethyl acetate/hexane to give **67h** as a colourless oil (80 mg, 27%). R_f = 0.20 (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{22}FNO_2 - C(CH_3)_3$: 236.1087; found 236.1080. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23-1.53 [9H, m, *^{t}Bu + ^{t}Bu], 1.57-1.77 [2H, m, H(5) + *H(5)], 2.35-2.46 [2H, m, H(4) + *H(4)], 3.46-3.56 [2H, m, H(6) + *H(6)], 3.97-4.12 [2H, m, H(2) + *H(2)], 6.27 [0.2H, br s, *H(A)], 6.34 [0.8H, br s, H(A)], 6.98-7.25 [4H, m, H(3') + *H(3') + H(4) + *H(4') + H(5') + *H(5') + H(6) + *H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 26.13 [br, C(5)], 26.98 [*C(5)], 27.98 [C(4)], 28.35 [br, *^{t}Bu], 28.62 [br, ^{t}Bu], 34.74 [br, *C(4)], 44.51 [br, C(6) + *C(6)], 50.58-53.47 [C(2) + *C(2)], 79.53 [*^{t}Bu], 79.72 [^{t}Bu], 115.14-115.68 [C(3') + *C(3')], 117.28-118.35 [C(A) + *C(A)], 123.08-124.11 [C(5') + *C(5')], 124.51-125.01 [C(1') + *C(1')], 128.20-128.79 [C(4') + *C(4')], 130.58-131.22 [C(6) + *C(6)], 138.58 [br, C(3) + *C(3)], 154.71 [*C=O], 154.96 [C=O], 159.08-161.47 [C(2') + *C(2')].

* denotes *Z*-isomer

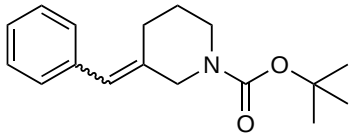
tert-Butyl 3-(4-fluorobenzylidene)piperidine-1-carboxylate (67j)



Using General Method 2, **36j** (0.74 g, 3.0 mmol), *N*-Boc-3-piperidone (0.30 g, 1.5 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.48 g, 12.0 mmol) were reacted in THF (5 mL) for 48 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **67j** as a colourless oil (101 mg, 23%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{22}FNO_2 - C(CH_3)_3$: 236.1087; found 236.1084. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 [2.7H, br s, *^{t}Bu], 1.48 [6.3H, s, ^{t}Bu], 1.57-1.65 [1.4H, m, H(5)], 1.68-1.75 [0.6H, m, *H(5)], 2.36-2.41 [0.6H, m, *H(4)], 2.45-2.50 [1.4H, m, H(4)], 3.47-3.53 [2H, m, H(6) + *H(6)], 4.00 [1.4H, br s, H(2)], 4.14 [0.6H, br s, *H(2)], 6.27 [0.3H, br s, *H(A)], 6.36 [0.7H, br s, H(A)], 6.97-7.05 [2H, m, H(3') + H(5') + *H(3') + *H(5')], 7.14-7.24 [2H, m, H(2') + H(6') + *H(2) + *H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 26.06 [C(5)], 26.93 [br, *C(5)], 27.39 [C(4)], 28.43 [br s, *^{t}Bu], 28.62 [^{t}Bu], 34.78 [br, *C(4)], 44.47 [br, C(6) + *C(6)], 45.89 [br, *C(2)], 51.57 [br, C(2)], 79.59 [*^{t}Bu], 79.68 [^{t}Bu], 115.16 [d, $^2J_{C,F}$ = 21.3 Hz, C(3') + C(5') + *C(3') + *C(5')], 123.54-124.36 [m, C(A) + *C(A)], 130.35-130.68 [m, C(2') + C(6') + *C(2') + *C(6')], 133.19 [d, $^4J_{C,F}$ = 3.3 Hz, C(1') + *C(1')], 136.23 [br, C(3) + *C(3)], 154.90 [C=O + *C=O], 160.58-162.73 [m, C(4') + *C(4')].

This data is consistent with that reported previously.[127]

tert-Butyl 3-benzylidenepiperidine-1-carboxylate (67x)

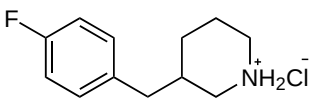


Synthesis method a. Using General Method 2, **36x** (0.75 g, 3.3 mmol), *N*-Boc-3-piperidone (0.33 g, 1.7 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.50 g, 12.5 mmol) were reacted in THF (5 mL) for 48 hr. The crude product was purified by column chromatography on silica gel eluting with 3:7 ethyl acetate/hexane to give **67x** as a colourless oil (214 mg, 47%). $R_f = 0.29$ (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{23}NO_2 - C(CH_3)_3$: 218.1181; found 218.1174. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 [2.7H, br s, *^{t}Bu], 1.48 [6.3H, s, ^{t}Bu], 1.61 [1.4H, br p, $^3J_{4,5} = {}^3J_{5,6} = 6.0$ Hz, H(5)], 1.72 [0.6H, br p, $^3J_{4,5} = {}^3J_{5,6} = 6.0$ Hz, *H(5)], 2.40 [0.6H, td, $^3J_{4,5} = 6.0$ Hz, $^4J_{4,6} = 1.0$ Hz, *H(4)], 2.52 [1.4H, td, $^3J_{4,5} = 6.0$ Hz, $^4J_{4,6} = 1.0$ Hz, H(4)], 3.46-3.54 [2H, m, H(6) + *H(6)], 4.01 [1.4H, br s, H(2)], 4.18 [0.6H, br s, *H(2)], 6.33 [0.3H, br s, *H(A)], 6.41 [0.7H, br s, H(A)], 7.17-7.26 [3H, m, H(2') + *H(2') + H(4') + *H(4') + H(6') + *H(6')], 7.29-7.35 [2H, m, H(3') + *H(3') + H(5') + *H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 26.13 [C(5)], 27.02 [br, *C(5)], 27.49 [C(4)], 28.42 [br s, *^{t}Bu], 28.64 [^{t}Bu], 34.90 [br, *C(4)], 44.54 [br, C(6) + *C(6)], 46.00 [br, *C(2)], 52.28 [br, C(2)], 79.53 [*^{t}Bu], 79.65 [^{t}Bu], 125.04 [br, C(A) + *C(A)], 126.64 [br, *C(4')], 126.66 [C(4')], 128.28 [C(3') + *C(3') + C(5') + *C(5')], 128.93 [*C(2') + *C(6')], 129.03 [C(2') + C(6')], 136.29 [br, C(3) + *C(3)], 137.27 [br, C(1') + *C(1')], 154.94 [C=O], 155.05 [br, *C=O].

*denotes *Z*-isomer

Synthesis method b. Bromobenzene (100 mg, 0.64 mmol) and **14** (25 mg, 0.13 mmol) were combined with potassium carbonate (53 mg, 0.38 mmol), tri-*o*-tolylphosphine (2.7 mg, 8.9 μmmol) and $Pd(OAc)_2$ (1.4 mg, 6.3 μmmol) in DMF (2 mL) and the mixture was stirred at 80°C for 48 hours. The mixture was cooled and filtered through Celite® washing with methanol, and the solvent was removed by evaporation under reduced pressure to give an brown residue. ^{1}H NMR analysis of crude mixture did not identify signals corresponding to the desired product.

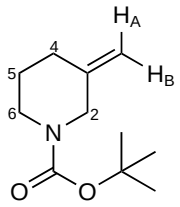
3-(4-Fluorobenzyl)piperidine hydrochloride (38j)



Using General Method 5, **36j** (0.50 g, 2.0 mmol), *N*-Boc-3-piperidone (0.20 g, 1.0 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.32 g, 8.0 mmol) were reacted for 48 hr

in THF (5 mL), then with Pd-C catalyst in methanol (20 mL) for 2 hr followed by hydrogen chloride solution (1M in diethyl ether, 1.5 mL) in diethyl ether (3 mL). A brown gum formed which was isolated by filtration. HRMS and ^{1}H NMR analysis indicated product was present in gum but could not be isolated.

tert-Butyl 3-methylenepiperidine-1-carboxylate (70)

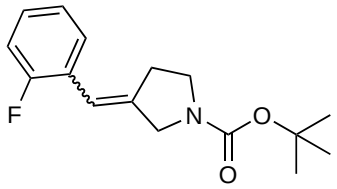


Synthesis method a. Anhydrous THF (4 mL) was added to methyltriphenylphosphonium bromide (0.54 g, 1.5 mmol) under an N_2 atmosphere. The mixture was cooled to -78°C and *n*-BuLi (2M in hexanes, 1.5 mL, 3.0 mmol) was added dropwise. The mixture was stirred for 30 min then solution of *N*-Boc-3-piperidone (0.20 g, 1.00 mmol) in THF was added over 5 min before the mixture was warmed to room temperature and stirred for 48 hr. The mixture was quenched with brine and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$, filtered, and solvent removed by evaporation under reduced pressure. Only starting materials were recovered.

Synthesis method b. Anhydrous THF (6 mL) was added to a mixture of methyltriphenylphosphonium bromide (0.32 g, 0.90 mmol) and sodium hydride (60% in mineral oil, 0.16 g, 4.0 mmol) under an N_2 atmosphere and the mixture was stirred for 30 min. A solution of *N*-Boc-3-piperidone (0.10 g, 0.50 mmol) in THF was added and the mixture stirred for 48 hr then quenched with brine solution (25 mL) and extracted with ethyl acetate (3 x 30 mL). The organic extracts were dried over $MgSO_4$, filtered, and solvent removed by evaporation under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate/hexane (1:1) to give a crude mixture containing **70** as an orange oil (12 mg, $<$12%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 [9H, s, ^{t}Bu], 1.58-1.66 [2H, m, H(5)], 2.23-2.29 [2H, m, H(4)], 3.39-3.48 [2H, m, H(6)], 3.87 [2H, br s, H(2)], 4.75 [1H, s, H(A)], 4.82 [1H, br s, H(B)].

This data is consistent with that reported previously.[128]

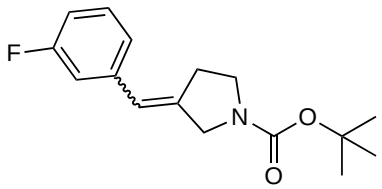
tert-Butyl 3-(2-fluorobenzylidene)pyrrolidine-1-carboxylate (68h)



Using General Method 2, **36h** (0.80 g, 3.2 mmol), *N*-Boc-3-pyrrolidinone (0.31 g, 1.7 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.26 g, 6.5 mmol) were reacted in THF (5 mL) for 48 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **68h** as a colourless oil (38 mg, 8%). $R_f = 0.24$ (9:1 hexane/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42-1.50 [9H, m, ^{t}Bu + *^{t}Bu], 2.45-2.59 [2H, m, H(4a) + H(4b) + *H(4a) + *H(4b)], 3.33-3.45 [2H, m, H(2a) + H(2b) + *H(2a) + *H(2b)], 3.62-3.78 [2H, m, H(5a) + H(5b) + *H(5a) + *H(5b)], 6.19-6.33 [1H, m, H(A) + *H(A)], 6.95-7.12 [2H, m, H(3') + H(5') + *H(3') + *H(5')], 7.13-7.24 [2H, m, H(2') + H(6') + *H(2') + *H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): 27.80-28.07 [m, C(2) + *C(2)], 28.44-28.73 [m, ^{t}Bu + *^{t}Bu], 31.09 [C(4)], 32.33 [*C(4)], 45.42 [C(5)], 45.92 [*C(5)], 79.88 [*^{t}Bu], 80.09 [^{t}Bu], 115.30-115.58 [m, C(3') + *C(3')], 124.09-124.25 [m, C(5') + *C(5')], 125.37-125.60 [m, C(A) + *C(A)], 126.12-126.35 [m, C(1') + *C(1')], 128.05-128.26 [m, C(4') + *C(4')], 130.85 [br‡, C(6')], 130.99 [br‡, *C(6')], 141.21-141.35 [m, C(3) + *C(3)], 151.49-151.77 [m, C=O + *C=O], 159.96-162.36 [m, C(2') + *C(2')].

* denotes signals corresponding to minor isomer.

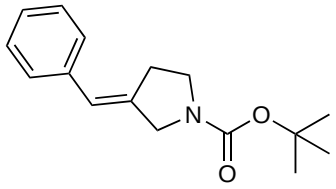
tert-Butyl 3-(3-fluorobenzylidene)pyrrolidine-1-carboxylate (68i)



Using General Method 2, **36i** (0.66 g, 2.7 mmol), *N*-Boc-3-pyrrolidinone (0.25 g, 1.3 mmol), and sodium hydride (60% dispersion in paraffin oil, 0.43 g, 10.8 mmol) were reacted in THF (5 mL) for 48 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **68i** as a colourless oil (7 mg, 4%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41-1.55 [9H, m, ^{t}Bu + *^{t}Bu], 2.38-2.55 [2H, m, H(4a) + H(4b) + *H(4a) + *H(4b)], 3.21-3.50 [2H, m, H(2a) + H(2b) + *H(2a) + *H(2b)], 3.63-3.79 [2H, m, H(5a) + H(5b) + *H(5a) + *H(5b)], 6.22-6.39 [1H, m, H(A) + *H(A)], 6.84-7.01 [3H, m, H(2') + H(4') + H(6') + *H(2') + *H(4') + *H(6')], 7.19-7.29 [1H, m, H(5') + *H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.44-28.73 [m, ^{t}Bu + *^{t}Bu], 30.92 [C(4)], 32.09 [*C(4)], 34.91

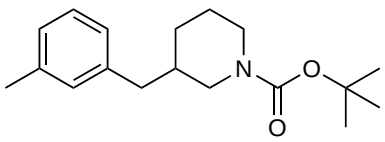
[C(2)], 34.98 [*C(2)], 45.42 [C(5)], 45.90 [*C(5)], 79.95 [*^{t}Bu], 80.16 [^{t}Bu], 113.04-113.50 [m, C(4') + *C(4')], 115.33-115.83 [m, C(3) + C(2') + *C(3) + *C(2')], 124.17-124.62 [m, C(A) + *C(A)], 125.51-125.82 [m, C(6') + *C(6')], 129.79-130.11 [m, C(5') + *C(5')], 141.78-141.99 [m, C(1') + *C(1')], 151.64 [*C=O], 152.33 [C=O], 161.87-164.25 [m, C(3') + *C(3')].

***tert*-Butyl 3-benzylidenepyrrolidine-1-carboxylate (68x)**



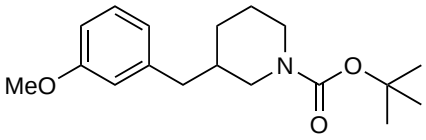
Using General Method 2, **36x** (1.85 g, 8.1 mmol), *N*-Boc-3-pyrrolidinone (0.75 g, 4.1 mmol), and sodium hydride (60% dispersion in paraffin oil, 1.29 g, 32.4 mmol) were reacted in THF (5 mL) for 48 hr. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give **68x** as a colourless oil (94 mg, 9%). $R_f = 0.22$ (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{21}NO_2$: 260.1651; found 260.1644. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39-1.53 [9H, m, ^{t}Bu + *^{t}Bu], 2.40-2.54 [2H, m, H(4a) + H(4b) + *H(4a) + *H(4b)], 3.22-3.50 [2H, m, H(2a) + H(2b) + *H(2a) + *H(2b)], 3.62-3.78 [2H, m, H(5a) + H(5b) + *H(5a) + *H(5b)], 6.21-6.37 [1H, m, H(A) + *H(A)], 7.13-7.36 [5H, m, Ph + *Ph].

***tert*-Butyl 3-(3-methylbenzyl)piperidine-1-carboxylate (69c)**



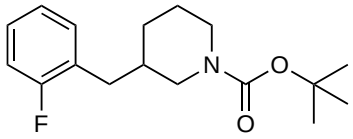
Using General Method 3, **67c** (156 mg, 0.54 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up gave crude **69c** as a colourless oil which was used without further purification (157 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{27}NO_2 - C(CH_3)_3$: 234.1494; found 234.1487. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94-1.25 [1H, m, $H(4_{ax})$], 1.27-1.55 [10H, m, ^{t}Bu + $H(5_{ax})$], 1.54-1.84 [3H, m, $H(3_{ax})$ + $H(4_{eq})$ + $H(5_{eq})$], 2.18-2.92 [7H, m, CH_3 + H(A) + H(A') + $H(2_{ax})$ + $H(6_{ax})$], 3.68-4.18 [2H, m, $H(2_{eq})$ + $H(6_{eq})$], 6.91-7.03 [3H, m, H(2') + H(4') + H(6')], 7.16 [1H, t, $^3J_{4',5'} = {}^3J_{5',6'} = 7.5$ Hz, H(5')].

tert-Butyl 3-(3-methoxybenzyl)piperidine-1-carboxylate (69f)



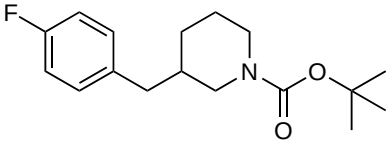
Using General Method 3, **67f** (85 mg, 0.28 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up gave crude **69f** as a colourless oil which was used without further purification (86 mg, 100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04-1.19 [1H, m, H(4_{ax})], 1.32-1.53 [10H, m, ^{t}Bu + H(5_{ax})], 1.58-1.66 [1H, m, H(4_{eq})], 1.68-1.80 [2H, m, H(3_{ax}) + H(5_{eq})], 2.32-2.68 [3H, m, H(A) + H(A') + H(2_{ax})], 2.69-2.88 [1H, m, H(6_{ax})], 3.74-4.12 [5H, m, H(2_{eq}) + H(6_{eq}) + OCH_3], 6.67-6.78 [3H, m, H(2') + H(4') + H(6')], 7.19 [1H, t, $^3J_{4',5'} = {}^3J_{5',6'} = 7.8$ Hz, H(5')].

tert-Butyl 3-(2-fluorobenzyl)piperidine-1-carboxylate (69h)



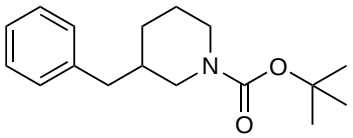
Using General Method 3, **67h** (64 mg, 0.22 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up and column chromatography on silica gel eluting with 9:1 hexane/ethyl acetate gave **69h** as a colourless oil (45 mg, 70%). R_f = 0.35 (9:1 hexane/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.07-1.22 [1H, m, H(4_{ax})], 1.30-1.53 [10H, m, ^{t}Bu + H(5_{ax})], 1.57-1.68 [1H, m, H(4_{eq})], 1.70-1.82 [2H, m, H(3_{ax}) + H(5_{eq})], 2.40-2.67 [3H, m, H(A) + H(A') + H(2_{ax})], 2.69-2.86 [1H, m, H(6_{ax})], 3.68-4.15 [2H, m, H(2_{eq}) + H(6_{eq})], 7.00 [1H, br dd‡, $^3J_{3',F} = 9.4$ Hz, $^3J_{3',4'} = 8.5$ Hz, H(3')], 7.05 [1H, br t, $^3J_{4',5'} = {}^3J_{5',6'} = 7.7$ Hz, H(5')], 7.12-7.21 [2H, m, H(4') + H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.96 [br, C(5)], 28.54 [^{t}Bu], 30.75 [C(4)], 33.13 [br, C(3)], 36.89 [br‡, C(A)], 44.58 [br, C(6)], 49.53 [br, C(2)], 79.34 [^{t}Bu], 115.34 [d, $^2J_{C,F} = 22.3$ Hz, C(3')], 123.96 [d, $^4J_{C,F} = 3.5$ Hz, C(5')], 126.91 [d, $^2J_{C,F} = 15.8$ Hz, C(1')], 127.88 [d, $^3J_{C,F} = 8.2$ Hz, C(4')], 131.43 [d, $^3J_{C,F} = 4.0$ Hz, C(6')], 154.99 [C=O], 161.34 [d, $^1J_{C,F} = 244.64$ Hz, C(2')].

tert-Butyl 3-(4-fluorobenzyl)piperidine-1-carboxylate (69j)



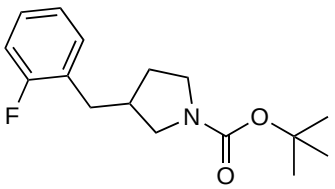
Using General Method 3, **67j** (101 mg, 0.35 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up and column chromatography on silica gel eluting with 9:1 hexane/ethyl acetate gave **69j** as a colourless oil (99 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02-1.20 [1H, m, H(4_{ax})], 1.31-1.52 [10H, m, ^{t}Bu + H(5_{ax})], 1.58-1.79 [3H, m, H(3_{ax}) + H(4_{eq}) + H(5_{eq})], 2.32-2.90 [4H, m, H(A) + H(A') + H(2_{ax}) + H(6_{ax})], 3.69-4.13 [2H, m, H(2_{eq}) + H(6_{eq})], 6.93-6.99 [2H, m, H(3') + H(5')], 7.07-7.13 [2H, m, $^{2}J_{C,F}$ = 21.2 Hz, H(2') + H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.00 [br, C(5)], 28.55 [^{t}Bu], 30.72 [br, C(4)], 37.91 [br‡, C(A)], 39.38 [br, C(3)], 44.54 [br, C(6)], 49.55 [br, C(2)], 79.42 [^{t}Bu], 115.13 [d, $^{3}J_{C,F}$ = 21.2 Hz, C(3') + C(5')], 130.44 [d, $^{3}J_{C,F}$ = 7.8 Hz, C(2') + C(6')], 135.65 [br‡, C(1')], 155.01 [C=O], 161.50 [d, $^{1}J_{C,F}$ = 243.70 Hz, C(4')].

***tert*-Butyl 3-benzylpiperidine-1-carboxylate (69x)**



Using General Method 3, **67x** (197 mg, 0.72 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up gave crude **69x** as a colourless oil which was used without further purification (198 mg, 100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02-1.21 [1H, m, H(4_{ax})], 1.31-1.53 [10H, m, ^{t}Bu + H(5_{ax})], 1.58-1.82 [3H, m, H(3_{ax}) + H(4_{eq}) + H(5_{eq})], 2.33-2.89 [4H, m, H(A) + H(A') + H(2_{ax}) + H(6_{ax})], 3.70-4.14 [2H, m, H(2_{eq}) + H(6_{eq})], 7.11-7.23 [3H, m, H(2') + H(4') + H(6')], 7.23-7.34 [2H, m, H(3') + H(5')].

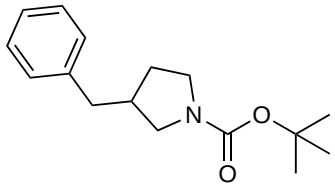
***tert*-Butyl 3-(2-fluorobenzyl)pyrrolidine-1-carboxylate (71h)**



Using General Method 3, **68h** (25 mg, 0.09 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up gave **71h** as a colourless oil (25 mg, 99%). R_f = 0.22 (9:1 hexane/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34-1.69 [10H, m, ^{t}Bu] + H(4a)], 1.83-1.99 [1H, m, H(4b)], 2.37-2.52 [1H, m, H(3)], 2.61-2.80 [2H, m, H(A) + H(A')], 2.92-3.07 [1H, m, H(2a)], 3.18-3.34 [1H, m, H(5a)], 3.34-3.57 [2H, m, H(2b) + H(5b)], 6.95-7.12 [2H, m, H(3') + H(5')], 7.11-7.25 [2H, m, H(4') + H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.42-28.79 [m, ^{t}Bu], 30.59-31.66 [m, C(4)], 32.25-32.44 [m, C(A)], 38.57-40.07 [m, C(3)], 44.94-45.95 [m, C(5)], 50.69-51.59 [m, C(2)], 79.05-79.24 [m,

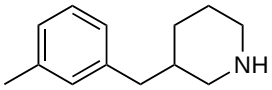
^{t}Bu], 115.26-115.60 [m, C(3')], 124.08-124.17 [m, C(5')], 127.16-127.45 [m, C(1')], 127.93-128.20 [m, C(4')], 130.99-131.19 [m, C(6')], 154.64-154.81 [m, C=O], 160.11-162.42 [m, C(2')].

tert-Butyl 3-benzylpyrrolidine-1-carboxylate (71x)



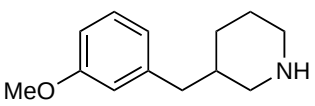
Using General Method 3, **68x** (94 mg, 0.36 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up gave crude **71x** as a colourless oil which was used without further purification (95 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{23}NO_2 - C(CH_3)_3$: 206.1181; found 206.1175. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40-1.50 [9H, m, ^{t}Bu], 1.53-1.63 [1H, m, H(4a)], 1.86-1.98 [1H, m, H(4b)], 2.32-2.49 [1H, m, H(3)], 2.59-2.75 [2H, m, H(A) + H(A')], 2.92-3.06 [1H, m, H(2a)], 3.16-3.33 [1H, m, H(5a)], 3.36-3.58 [2H, m, H(2b) + H(5b)], 7.09-7.36 [5H, m, H(2') + H(3') + H(4') + H(5') + H(6')].

3-(3-Methylbenzyl)piperidine (32c)



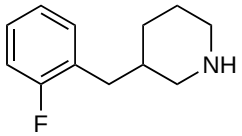
Using General Method 4, **69c** (157 mg, 0.54 mmol) and trifluoroacetic acid (2 mL) were reacted in dichloromethane (8 mL) to give **32c** as a yellow oil (101 mg, 98%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.11 [1H, qd, $^2J_{4ax,4eq} = {}^3J_{3ax,4ax} = {}^3J_{4ax,5ax} = 12.7$ Hz, $^3J_{4ax,5eq} = 3.6$ Hz, H(4_{ax})], 1.58 [1H, qt, $^2J_{5ax,5eq} = {}^3J_{4ax,5ax} = {}^3J_{5ax,6ax} = 12.7$ Hz, $^3J_{4eq,5ax} = {}^3J_{5ax,6eq} = 3.6$ Hz, H(5_{ax})], 1.73 [1H, br d‡, $^2J_{5ax,5eq} = 12.7$ Hz, H(5_{eq})], 1.82 [1H, br d‡, $^2J_{4ax,4eq} = 12.7$ Hz, H(4_{eq})], 1.91 [1H, ttt, $^3J_{2ax,3ax} = {}^3J_{3ax,4ax} = 12.7$ Hz, $^3J_{3ax,A} = {}^3J_{3ax,A'} = 7.4$ Hz, $^3J_{2eq,3ax} = {}^3J_{3ax,4eq} = 3.6$ Hz, H(3_{ax})], 2.32 [3H, s, CH_3], 2.38 [1H, dd, $^3J_{2ax,3ax} = 12.7$ Hz, $^2J_{2ax,2eq} = 11.4$ Hz, H(2_{ax})], 2.42-2.53 [2H, m, H(A) + H(A')], 2.62 [1H, td, $^2J_{6ax,6eq} = {}^3J_{5ax,6ax} = 12.7$ Hz, $^3J_{5eq,6ax} = 3.6$ Hz, H(6_{ax})], 3.05-3.15 [2H, m, H(2_{eq}) + H(6_{eq})], 4.90 [1H, br s, NH], 6.89-6.97 [2H, m, H(2') + H(4')], 7.01 [1H, br d‡, $^3J_{5',6'} = 7.5$ Hz, H(6')], 7.16 [1H, t, $^3J_{4',5'} = {}^3J_{5',6'} = 7.5$ Hz, H(5')].

3-(3-Methoxybenzyl)piperidine (32f)



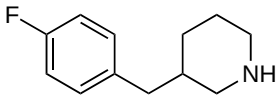
Using General Method 4, **69f** (96 mg, 0.31 mmol) and trifluoroacetic acid (1 mL) were reacted in dichloromethane (4 mL) to give crude **32f** as a yellow oil which was used without further purification (61 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 [1H, qd, $^2J_{4ax,4eq}$ = $^3J_{3ax,4ax}$ = $^3J_{4ax,5ax}$ = 12.7 Hz, $^3J_{4ax,5eq}$ = 3.5 Hz, H(4_{ax})], 1.59 [1H, qt, $^2J_{5ax,5eq}$ = $^3J_{4ax,5ax}$ = $^3J_{5ax,6ax}$ = 12.7 Hz, $^3J_{4eq,5ax}$ = $^3J_{5ax,6eq}$ = 3.5 Hz, H(5_{ax})], 1.67 [1H, br d‡, $^2J_{5ax,5eq}$ = 12.7 Hz, H(5_{eq})], 1.72-1.86 [2H, m, H(3_{ax}) + H(4_{eq})], 2.32 [1H, dd, $^3J_{2ax,3ax}$ = 12.7 Hz, $^2J_{2ax,2eq}$ = 11.0 Hz, H(2_{ax})], 2.44 and 2.48 [2H, *ABX*, *A*:dd, *B*:dd, $^2J_{A,A'}$(J_{AB}) = 13.6 Hz, $^3J_{A,3'ax}$(J_{AX}) = 7.1 Hz, $^3J_{A',3'ax}$(J_{BX}) = 7.2 Hz, H(A) + H(A')], 2.56 [1H, td, $^2J_{6ax,6eq}$ = $^3J_{5ax,6ax}$ = 12.7 Hz, $^3J_{5eq,6ax}$ = 2.7 Hz, H(6_{ax})], 2.99-3.08 [2H, m, H(2_{eq}) + H(6_{eq})], 3.48 [1H, br s, NH], 3.79 [3H, s, OCH_3], 6.69 [1H, br s‡, H(2')], 6.70-6.77 [2H, m, H(4') + H(6')], 7.18 [1H, t, $^3J_{4',5'}$ = $^3J_{5',6'}$ = 7.9 Hz, H(5')].

3-(2-Fluorobenzyl)piperidine (32h)



Using General Method 4, **69h** (33 mg, 0.11 mmol) and trifluoroacetic acid (1 mL) were reacted in dichloromethane (4 mL) to give crude **32h** as a yellow oil which was used without further purification (20 mg, 92%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{12}H_{16}FN$: 194.1345; found 194.1341. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 [1H, qd, $^2J_{4ax,4eq}$ = $^3J_{3ax,4ax}$ = $^3J_{4ax,5ax}$ = 12.5 Hz, $^3J_{4ax,5eq}$ = 3.5 Hz, H(4_{ax})], 1.59 [1H, qt, $^2J_{5ax,5eq}$ = $^3J_{4ax,5ax}$ = $^3J_{5ax,6ax}$ = 12.5 Hz, $^3J_{4eq,5ax}$ = $^3J_{5ax,6eq}$ = 3.5 Hz, H(5_{ax})], 1.73 [1H, br d‡, $^2J_{5ax,5eq}$ = 12.5 Hz, H(5_{eq})], 1.81 [1H, br d‡, $^2J_{4ax,4eq}$ = 12.5 Hz, H(4_{eq})], 1.94 [1H, ttt, $^3J_{2ax,3ax}$ = $^3J_{3ax,4ax}$ = 12.5 Hz, $^3J_{3ax,A}$ = $^3J_{3ax,A'}$ = 7.3 Hz, $^3J_{2eq,3ax}$ = $^3J_{3ax,4eq}$ = 3.5 Hz, H(3_{ax})], 2.42 [1H, t, $^2J_{2ax,2eq}$ = $^3J_{2ax,3ax}$ = 12.5 Hz, H(2_{ax})], 2.48-2.66 [3H, m, H(A) + H(A') + H(6_{ax})], 3.06-3.18 [2H, m, H(2_{eq}) + H(6_{eq})], 6.08 [1H, br s, NH], 6.96-7.08 [2H, m, H(3') + H(5')], 7.09-7.22 [2H, m, H(4') + H(6')].

3-(4-Fluorobenzyl)piperidine (32j)

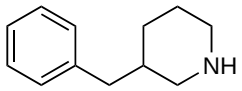


Using General Method 4, **69j** (99 mg, 0.34 mmol) and trifluoroacetic acid (1 mL) were reacted in dichloromethane (4 mL) to give **32j** as a yellow oil (60 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 [1H, qd, $^2J_{4ax,4eq}$ = $^3J_{3ax,4ax}$ = $^3J_{4ax,5ax}$ = 12.4 Hz, $^3J_{4ax,5eq}$ = 3.5 Hz, H(4_{ax})], 1.64 [1H, qt, $^2J_{5ax,5eq}$ = $^3J_{4ax,5ax}$ = $^3J_{5ax,6ax}$ = 12.4 Hz, $^3J_{4eq,5ax}$ = $^3J_{5ax,6eq}$ = 3.5 Hz, H(5_{ax})], 1.73-1.85 [2H, m, H(4_{eq}) + H(5_{eq})], 1.96 [1H, ttt, $^3J_{2ax,3ax}$ = $^3J_{3ax,4ax}$ = 12.4 Hz, $^3J_{3ax,A}$ =

$^{3}J_{3ax,A'}$ = 7.5 Hz, $^{3}J_{2eq,3ax}$ = $^{3}J_{3ax,4eq}$ = 3.5 Hz, H(3_{ax})], 2.41 [1H, t, $^{2}J_{2ax,2eq}$ = $^{3}J_{2ax,3ax}$ = 12.4 Hz, H(2_{ax})], 2.47-2.53 [2H, m, H(A) + H(A')], 2.65 [1H, td, $^{2}J_{6ax,6eq}$ = $^{3}J_{5ax,6ax}$ = 12.5 Hz, $^{3}J_{5eq,6ax}$ = 3.5 Hz, H(6_{ax})], 3.10 [1H, br d‡, $^{2}J_{2ax,2eq}$ = 12.4 Hz, H(2_{eq})], 3.16 [1H, br d‡, $^{2}J_{6ax,6eq}$ = 12.4 Hz, H(6_{eq})], 6.75 [1H, br s, NH], 6.93-7.00 [2H, m, H(3') + H(5')], 7.04-7.11 [2H, m, H(2') + H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 23.69 [C(5)], 29.78 [C(4)], 36.60 [C(3)], 39.73 [C(A)], 45.18 [C(6)], 50.09 [C(2)], 115.40 [d, $^{2}J_{C,F}$ = 21.1 Hz, C(3) + C(5)], 130.44 [d, $^{3}J_{C,F}$ = 7.8 Hz, C(2) + C(6)], 134.44 [d, $^{4}J_{C,F}$ = 3.4 Hz, C(1)], 161.68 [d, $^{1}J_{C,F}$ = 244.3 Hz, C(4)].

This data is consistent with that reported in literature.[129]

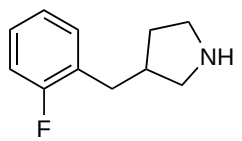
3-Benzylpiperidine (32x)



Using General Method 4, **69x** (229 mg, 0.83 mmol) and trifluoroacetic acid (2 mL) were reacted in dichloromethane (8 mL) to give **32x** as a yellow oil (141 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.11 [1H, qd, $^{2}J_{4ax,4eq}$ = $^{3}J_{3ax,4ax}$ = $^{3}J_{4ax,5ax}$ = 12.5 Hz, $^{3}J_{4ax,5eq}$ = 3.7 Hz, H(4_{ax})], 1.57 [1H, qt, $^{2}J_{5ax,5eq}$ = $^{3}J_{4ax,5ax}$ = $^{3}J_{5ax,6ax}$ = 12.5 Hz, $^{3}J_{4eq,5ax}$ = $^{3}J_{5ax,6eq}$ = 3.7 Hz, H(5_{ax})], 1.72 [1H, br d‡, $^{2}J_{5ax,5eq}$ = 12.5 Hz, H(5_{eq})], 1.81 [1H, br d‡, $^{3}J_{4eq,5ax}$ = 12.5 Hz, H(4_{eq})], 1.90 [1H, ttt, $^{3}J_{2ax,3ax}$ = $^{3}J_{3ax,4ax}$ = 12.5 Hz, $^{3}J_{3ax,A}$ = $^{3}J_{3ax,A'}$ = 7.4 Hz, $^{3}J_{2eq,3ax}$ = $^{3}J_{3ax,4eq}$ = 3.7 Hz, H(3_{ax})], 2.38 [1H, t, $^{2}J_{2ax,2eq}$ = $^{3}J_{2ax,3ax}$ = 12.5 Hz, H(2_{ax})], 2.46-2.55 [2H, m, H(A) + H(A')], 2.61 [1H, br t‡, $^{2}J_{6ax,6eq}$ = $^{3}J_{5ax,6ax}$ = 12.5 Hz, H(6_{ax})], 3.03-3.15 [2H, m, H(2_{eq}) + H(6_{eq})], 5.92 [1H, br s, NH], 7.09-7.15 [2H, m, H(2') + H(6')], 7.19 [1H, br t‡, $^{3}J_{3',4'}$ = $^{3}J_{4',5'}$ = 7.3 Hz, H(4')], 7.24-7.31 [2H, m, H(3') + H(5')].

This data is consistent with that reported in literature.[130]

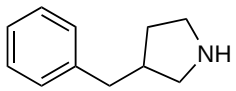
3-(2-Fluorobenzyl)pyrrolidine (33h)



Using General Method 4, **71h** (19 mg, 0.07 mmol) and trifluoroacetic acid (1 mL) were reacted in dichloromethane (4 mL) to give **33h** as an orange oil (4 mg, 33%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.67 [1H, dq, $^{2}J_{4a,4b}$ = 13.0 Hz, $^{3}J_{3,4a}$ = $^{3}J_{4a,5a}$ = $^{3}J_{4a,5b}$ = 8.0 Hz, H(4a)], 2.01 [1H, dtd, $^{2}J_{4a,4b}$ = 13.0 Hz, $^{3}J_{4b,5a}$ = $^{3}J_{3,4b}$ = 8.0 Hz, $^{3}J_{4b,5b}$ = 4.6 Hz, H(4b)], 2.54 [1H, septet, $^{3}J_{3,A}$ = $^{3}J_{3,A'}$ = $^{3}J_{2a,3}$ = $^{3}J_{2b,3}$ = $^{3}J_{3,4a}$ = $^{3}J_{3,4b}$ = 8.0 Hz, H(3)], 2.67-2.83 [3H, m, H(A) + H(A') + H(2a)], 3.10 [2H, dt, $^{2}J_{5a,5b}$ = 11.1 Hz, $^{3}J_{4a,5a}$ = $^{3}J_{4b,5a}$ = 8.0

Hz, H(5a)], 3.16-3.29 [2H, m, H(2b) + H(5b)], 7.02 [1H, dd, $^{3}J_{3',F} = 9.6$ Hz, $^{3}J_{3',4'} = 8.7$ Hz, H(3')], 7.06 [1H, t, $^{3}J_{4',5'} = {}^{3}J_{5',6'} = 7.5$ Hz, H(5')], 7.11-7.24 [2H, m, H(4') + H(6')], 7.32 [1H, br s, NH]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.07 [C(4)], 32.38 [d, $^{3}J_{C,F} = 1.7$ Hz, C(A)], 39.51 [C(3)], 45.27 [C(5)], 50.58 [C(2)], 115.55 [d, $^{2}J_{C,F} = 22.3$ Hz, C(3')], 124.30 [d, $^{4}J_{C,F} = 3.5$ Hz, C(5')], 126.79 [d, $^{2}J_{C,F} = 15.8$ Hz, C(1')], 128.38 [d, $^{3}J_{C,F} = 8.1$ Hz, C(4')], 131.10 [d, $^{3}J_{C,F} = 4.8$ Hz, C(6')], 161.18 [d, $^{1}J_{C,F} = 224.7$ Hz, C(2')].

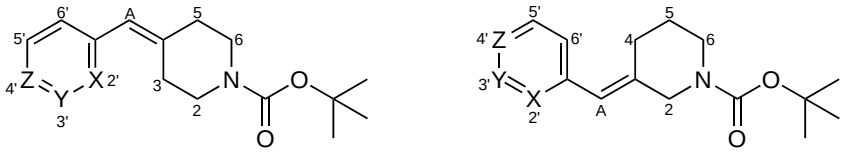
3-Benzylpyrrolidine (33x)



Using General Method 4, **71x** (95 mg, 0.36 mmol) and trifluoroacetic acid (1 mL) were reacted in dichloromethane (4 mL) to give **33x** as an orange oil (58 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{11}H_{15}N$: 162.1283; found 162.1279. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.67 [1H, dq, $^{2}J_{4a,4b} = 13.1$ Hz, $^{3}J_{3,4a} = {}^{3}J_{4a,5a} = {}^{3}J_{4a,5b} = 7.8$ Hz, H(4a)], 2.02-2.10 [1H, m, H(4b)], 2.57 [1H, septet, $^{3}J_{3,A} = {}^{3}J_{3,A'} = {}^{3}J_{2a,3} = {}^{3}J_{2b,3} = {}^{3}J_{3,4a} = {}^{3}J_{3,4b} = 7.8$ Hz, H(3)], 2.69-2.74 [2H, m, H(A) + H(A')], 2.83 [1H, dd, $^{2}J_{2a,2b} = 11.2$ Hz, $^{3}J_{2a,3} = 7.8$ Hz, H(2a)], 3.15 [1H, dt, $^{2}J_{5a,5b} = 11.3$ Hz, $^{3}J_{4a,5a} = {}^{3}J_{4b,5a} = 7.8$ Hz, H(5a)], 3.22-3.45 [3H, m, H(2b) + H(5b) + NH], 7.13-7.18 [2H, m, H(2') + H(6')], 7.22 [2H, t, $^{3}J_{3',4'} = {}^{3}J_{4',5'} = 7.2$ Hz, H(4')], 7.27-7.33 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.98 [C(4)], 39.12 [C(A)], 40.46 [C(3)], 45.28 [C(5)], 50.54 [C(2)], 126.42 [C(4')], 128.60 [C(2') + C(3') + C(5') + C(6')], 139.71 [C(1')].

6.2.4 Synthesis of pyridinylmethylpiperidine derivatives

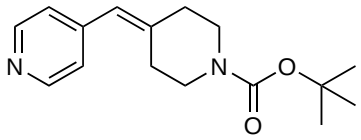
General Method 8: Synthesis of pyridinyl-extended piperidines via Wittig reaction



LiHMDS (1.0 M in THF, 2 eq) was added to a stirring suspension of the triphenylphosphonium halide Wittig reagent (1.4 eq) in THF under an atmosphere of nitrogen. The mixture was stirred for 15 min and a solution of the Boc-protected piperidone reagent (1 eq) in THF was then added dropwise. The reaction mixture was stirred for the specified time, then quenched with methanol (30 mL) and concentrated to dryness by evaporation under reduced pressure. The residue was suspended in ethyl acetate/hexane (2:3, 40 mL) then filtered to remove insoluble solid. The filtrate was concentrated to dryness by evaporation under reduced

pressure and the residue was purified by flash column chromatography on silica gel with the specified eluant.

***tert*-Butyl 4-(pyridin-4-ylmethylene)piperidine-1-carboxylate (53c)**



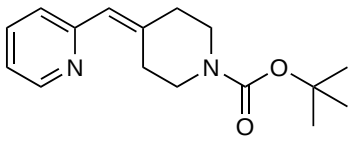
Synthesis method a. Using General Method 2, a sample of crude **50c** (74 mg, 0.32 mmol), *N*-Boc-4-piperidone (32 mg, 0.16 mmol), and sodium hydride (60% dispersion in paraffin oil, 38 mg, 0.96 mmol) were reacted in THF (5 mL) for 18 hr. Work-up and attempted purification of the crude product by column chromatography on silica gel eluting with 1:1 ethyl acetate/hexane gave a crude brown oil containing **53c**.

Synthesis method b. To a stirring mixture of **52c** (0.94 g, 2.2 mmol) in dry THF at -78°C under an atmosphere of nitrogen was added *n*-BuLi (2.0 M in hexanes, 3.3 mL, 6.6 mmol) dropwise over 10 min. The mixture was stirred for 15 min before dropwise addition of *N*-Boc-4-piperidone (0.33 g, 1.7 mmol) in THF. The reaction mixture was stirred a further 48 hr then quenched with water. The mixture was concentrated to dryness under reduced pressure and product purified by flash column chromatography on silica gel (1:1 ethyl acetate/hexane) to give the desired product **53c** as a pale yellow oil (240 mg, 53%*). $R_f = 0.25$ (1:1 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{22}N_2O_2$: 275.1760; found 275.1759. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.30-2.39 [2H, m, H(3)], 2.41-2.52 [2H, m, H(5)], 3.36-3.47 [2H, m, H(2)], 3.47-3.58 [2H, m, H(6)], 6.28 [1H, s, H(A)], 7.05-7.12 [2H, m, H(2') + H(6')], 8.49-8.59 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.58 [^{t}Bu], 29.49 [br, C(3)], 36.46 [br, C(5)], 43.52-46.51 [C(2) + C(6)], 79.91 [^{t}Bu], 122.46 [C(2') + C(6')], 123.82 [C(A)], 142.80 [C(4)], 145.20 [C(1')], 149.87 [C(3') + C(5')], 154.80 [C=O].

*Sample obtained from column chromatography contains triphenylphosphine oxide impurity. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.48 [m], 7.52-7.58 [m], 7.58-7.67 [m].

Synthesis method c. To a stirring mixture of **52c** (100 mg, 0.23 mmol) in dry THF under an atmosphere of nitrogen was added LiHMDS (1.0 M in THF, 400 μL, 0.40 mmol) dropwise over 10 min. The mixture was stirred for 15 min before dropwise addition of *N*-Boc-4-piperidone (35 mg, 0.18 mmol) in THF. The reaction mixture was stirred for 16 hr then quenched with water. The mixture was concentrated to dryness under reduced pressure, then resuspended in 1:1 ethyl acetate/hexane (50 mL) and filtered. The solvent was removed by evaporation under reduced pressure and the product purified by flash column chromatography on silica gel (1:1 ethyl acetate/hexane) to give the desired product **53c** as a pale yellow oil (93 mg, 52%*). Data as above.

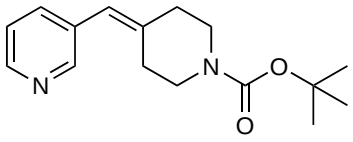
tert-Butyl 4-(pyridin-2-ylmethylene)piperidine-1-carboxylate (53a)



Using General Method 8, **52a** (1.00 g, 2.3 mmol) was reacted with LiHMDS solution (1.0 M in THF, 3.0 mL, 3.0 mmol) and *N*-Boc-4-piperidone (0.33 g, 1.7 mmol) in THF (6 mL) for 4 hr. The crude product was purified by column chromatography on silica gel eluting with 1:1 ethyl acetate/hexane to give **53a** as a white solid (0.37 g, 81%*). R_f = 0.59 (1:1 ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 (9H, s, ^{t}Bu), 2.30-2.41 [2H, m, H(5)], 2.80-2.88 [2H, m, H(3)], 3.39-3.49 [2H, m, H(2)], 3.50-3.58 [2H, m, H(6)], 6.37 [1H, s, H(A)], 7.08 [1H, br dd‡, $^3J_{4',5'}$ = 7.6 Hz, $^3J_{3',4'}$ = 4.8 Hz, H(4')], 7.14 [1H, br d‡, $^3J_{5',6'}$ = 7.6 Hz, H(6')], 7.61 [1H, td, $^3J_{4',5'}$ = $^3J_{5',6'}$ = 7.6 Hz, $^4J_{3',5'}$ = 1.7 Hz, H(5')], 8.57 [1H, br d‡, $^3J_{3',4'}$ = 4.8 Hz, H(3')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.59 [^{t}Bu], 29.44 [br, C(3)], 36.77 [br, C(5)], 45.09 [br, C(2) + C(6)], 79.68 [^{t}Bu], 121.08 [C(4')], 124.16 [br, C(A) + C(6')], 136.14 [C(5')], 143.30 [br, C(4)], 149.31 [C(3')], 154.90 [C=O], 156.72 [C(1')].

*Sample obtained from column chromatography contains triphenylphosphine oxide impurity. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.48 [m], 7.52-7.58 [m], 7.58-7.67 [m].

tert-Butyl 4-(pyridin-3-ylmethylene)piperidine-1-carboxylate (53b)



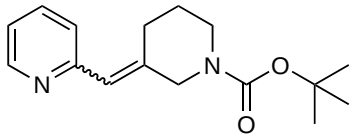
Synthesis method a. To a stirring mixture of **52b** (0.29 g, 0.75 mmol) in dry THF at -78°C under an atmosphere of nitrogen was added *n*-BuLi (2.0 M in hexanes, 1.0 mL, 2.0 mmol) dropwise over 10 min. The mixture was stirred for 15 min before dropwise addition of *N*-Boc-4-piperidone (0.10 g, 0.50 mmol) in THF. The reaction mixture was stirred at 0°C for 48 hr then quenched with water. The mixture was concentrated to dryness under reduced pressure and product purified by flash column chromatography on silica gel (20% - 100% ethyl acetate in hexane) to give the desired product **53b** as a pale yellow oil (50 mg, 36%*). R_f = 0.26 (1:1 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{22}N_2O_2$: 275.1760; found 275.1752. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.31-2.49 [4H, m, H(3) + H(5)], 3.35-3.46 [2H, m, H(2)], 3.48-3.57 [2H, m, H(6)], 6.30 [1H, s, H(A)], 7.25 [1H, dd, $^3J_{4',5'}$ = 4.9 Hz, $^3J_{5',6'}$ = 7.7 Hz, H(5')], 7.50 [1H, d, $^3J_{5',6'}$ = 7.7 Hz, H(6')], 8.45 [1H, d, $^3J_{4',5'}$ = 4.9 Hz, H(4')], 8.46 [1H, s, H(2')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.54 [^{t}Bu], 29.28 [br, C(3)], 36.32 [br, C(5)], 45.05 [br, C(2) + C(6)], 79.81 [^{t}Bu], 120.96 [C(5')], 123.17 [C(A)], 133.17 [C(1')], 136.06 [C(6')], 141.22 [C(4)], 147.50 [C(2')], 150.08 [C(4')], 154.78 [C=O].

*Sample obtained from column chromatography contains triphenylphosphine oxide impurity. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.48 [m], 7.52-7.58 [m], 7.58-7.67 [m].

Synthesis method b. 3-Bromopyridine (72 mg, 0.15 mmol), and **5** (30 mg, 0.15 mmol) were combined in DMF (2 mL) with potassium carbonate (63 mg, 0.46 mmol), tri-*o*-tolylphosphine (2.3 mg, 7.6 μmol) and $Pd(OAc)_2$ (1.4 mg, 6.2 μmol) and stirred at 80°C for 48 hr. Work up as specified gave an oil residue. ^{1}H NMR analysis of crude mixture indicated no **53b** present in mixture.

Synthesis method c. Using General Method 8, **52b** (0.82 g, 2.1 mmol) was reacted with LiHMDS (1.0 M in THF, 2.7 mL, 2.7 mmol) and *N*-Boc-4-piperidone (295 mg, 1.5 mmol) in THF (6 mL) for 16 hr. The crude residue was purified by flash column chromatography on silica gel (2:3 ethyl acetate/hexane) to give **53b** as a pale yellow oil (102 mg, 25%). Data as above.

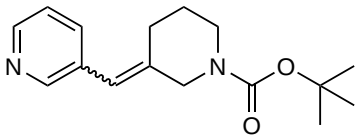
(*E/Z*)-*tert*-Butyl 3-(pyridin-2-ylmethylene)piperidine-1-carboxylate (75a)



Using General Method 8, **52a** (0.98 g, 2.3 mmol) was reacted with *N*-Boc-3-piperidone (0.30 g, 1.5 mmol) and LiHMDS solution (1M in THF, 3.0 mL, 3.0 mmol) in THF (8 mL) for 16 hr. Work-up and purification by column chromatography eluting with 2:3 ethyl acetate/hexane gave a mixture of (*E*/*Z*)-**75a** as a yellow oil (250 mg, 61%). $R_f = 0.36$ (2:3 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{22}N_2O_2$: 275.1760; found 275.1755. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 [4H, br s, *^{t}Bu], 1.47 [5H, s, ^{t}Bu], 1.67 [1.1H, p, $^3J_{4,5} = {}^3J_{5,6} = 5.5$ Hz, H(5)], 1.74 [0.9H, p, $^3J_{4,5} = {}^3J_{5,6} = 5.5$ Hz, *H(5)], 2.44 [0.9H, t, $^3J_{4,5} = 5.5$ Hz, *H(4)], 2.88 [1.1H, br s, H(4)], 3.51 [2H, br t, $^3J_{5,6} = 5.5$ Hz, H(6) + *H(6)], 4.05 [1.1H, s, H(2)], 4.57 [0.9H, br s, *H(2)], 6.34 [0.45H, s, *H(A)], 6.42 [0.55H, br s, H(A)], 7.06-7.13 [1H, m, H(4') + *H(4')], 7.18 [0.55H, d, $^3J_{5',6'} = 7.8$ Hz, H(6')], 7.21 [0.45H, br s, *H(6')], 7.59-7.67 [1H, m, H(5') + *H(5')], 8.58 [1H, d, $^3J_{3',4'} = 4.7$ Hz, H(3') + *H(3')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.85 [*C(3)], 26.76 [C(3)], 28.38 [br, *^{t}Bu], 28.57 [^{t}Bu], 35.03 [br, C(4) + *C(4)], 44.10 [C(6)], 45.90 [*C(6)], 51.57 [*C(2)], 52.88 [C(2)], 79.35 [*^{t}Bu], 79.62 [^{t}Bu], 121.19 [C(A)], 121.25 [*C(A)], 123.98 [C(4')], 124.38 [*C(4')], 136.10 [C(6')], 136.16 [*C(6')], 140.75 [C(5') + *C(5')], 149.25 [br, C(3') + *C(3')], 154.77 [C(3)], 154.88 [*C(3)], 156.13 [br, *C(1')], 156.45 [C(1')].

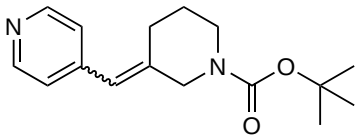
* denotes *Z*-isomer

(*E/Z*)-*tert*-Butyl 3-(pyridin-3-ylmethylene)piperidine-1-carboxylate (75b)



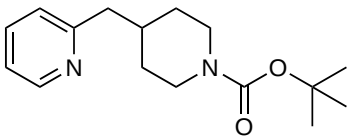
To a stirring mixture of **52b** (0.90 g, 2.3 mmol) in dry THF at -78°C under an atmosphere of nitrogen was added *n*-BuLi (2.0 M in hexanes, 3.0 mL, 3.0 mmol) dropwise over 10 min. The mixture was stirred for 15 min before dropwise addition of *N*-Boc-3-piperidone (0.30 g, 1.5 mmol) in THF. The reaction mixture was stirred at 0°C for 48 hr then quenched with water. The mixture was concentrated to dryness under reduced pressure to give a crude mixture. ^{1}H NMR analysis found the desired product **75b** was not present.

(*E/Z*)-*tert*-Butyl 3-(pyridin-4-ylmethylene)piperidine-1-carboxylate (75c)



Using General Method 8, **52c** (0.98 g, 2.3 mmol) was reacted with *N*-Boc-3-piperidone (0.30 g, 1.5 mmol) and LiHMDS (1M in THF, 3.0 mL, 3.0 mmol) in THF (8 mL) for 16 hr. Work-up gave a crude mixture, which was determined to contain none of the desired product by ^{1}H NMR analysis.

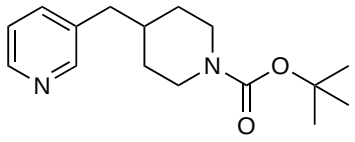
***tert*-Butyl 4-(pyridin-2-ylmethyl)piperidine-1-carboxylate (76a)**



Using General Method 3, **53a** (0.35 g, 1.3 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr to give **76a** as an orange oil (0.34 g, 96%*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq} = {}^{3}J_{(2/6)ax,(3/5)ax} = {}^{3}J_{(3/5)ax,4ax}$ = 12.0 Hz, $^{3}J_{(2/6)eq,(3/5)ax}$ = 3.9 Hz, H(3_{ax}) + H(5_{ax})], 1.45 [9H, s, ^{t}Bu], 1.61 [2H, br d‡, $^{2}J_{(3/5)ax,(3/5)eq}$ = 12.0 Hz, H(3_{eq}) + H(5_{eq})], 1.96 [1H, ttt, $^{3}J_{3ax,4ax} = {}^{3}J_{4ax,5ax}$ = 12.0 Hz, $^{3}J_{4ax,A}$ = 7.5 Hz, $^{3}J_{3eq,4ax} = {}^{3}J_{4ax,5eq}$ = 3.9 Hz, H(4_{ax})], 2.55-2.81 [4H, m, H(2_{ax}) + H(6_{ax}) + H(A)], 4.07 [2H, br s‡, H(2_{eq}) + H(6_{eq})], 7.06-7.17 [2H, m, H(4') + H(6')], 7.59 [1H, t, $^{3}J_{4',5'} = {}^{3}J_{5',6'}$ = 7.6 Hz, H(5')], 8.55 [1H, d, $^{3}J_{3',4'}$ = 4.9 Hz, H(3')].

*Sample contained impurities including triphenylphosphine oxide from previous reaction.

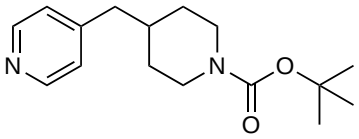
tert-Butyl 4-(pyridin-3-ylmethyl)piperidine-1-carboxylate (76b)



Using General Method 3, **53b** (40 mg, 0.15 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr to give **76b** as an orange oil which was used without further purification (39 mg, 97%*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 [2H, br q‡, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax}$ = 12.0 Hz, H(3_{ax}) + H(5_{ax})], 1.45 [9H, s, ^{t}Bu], 1.56-1.73 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.55 [2H, d, $^3J_{4ax,A}$ = 6.9 Hz, H(A)], 2.64 [2H, br t‡, $^2J_{(2/6)ax,(2/6)eq} = {}^3J_{(2/6)ax,(3/5)ax}$ = 12.0 Hz, H(2_{ax}) + H(6_{ax})], 4.08 [2H, br s‡, H(2_{eq}) + H(6_{eq})], 7.24 [1H, br dd‡, $^3J_{5',6'}$ = 7.7 Hz, $^3J_{4',5'}$ = 4.4 Hz, H(5')], 7.49 [1H, br d‡, $^3J_{5',6'}$ = 7.7 Hz, H(6')], 8.38 [1H, br s‡, H(2')], 8.42 [1H, br d‡, $^3J_{4',5'}$ = 4.4 Hz, H(4')].

*Sample contained impurities including triphenylphosphine oxide from previous reaction.

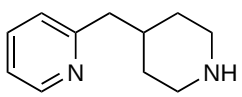
tert-Butyl 4-(pyridin-4-ylmethyl)piperidine-1-carboxylate (76c)



Using General Method 3, **53c** (240 mg, 0.87 mmol) in methanol (30 mL) was reacted with Pd-C catalyst under a hydrogen atmosphere for 2 hr. Work up afforded crude **76c** as an orange oil which was used without further purification (250 mg, 97%*). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{24}N_2O_2$: 277.1916; found 277.1910. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 [2H, br q‡, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax}$ = 12.2 Hz, H(3_{ax}) + H(5_{ax})], 1.45 [9H, s, ^{t}Bu], 1.53-1.76 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.53 [2H, d, $^3J_{4ax,A}$ = 7.1 Hz, H(A)], 2.64 [2H, br t‡, $^2J_{(2/6)ax,(2/6)eq} = {}^3J_{(2/6)ax,(3/5)ax}$ = 12.2 Hz, H(2_{ax}) + H(6_{ax})], 4.08 [2H, br s‡, H(2_{eq}) + H(6_{eq})], 6.98-7.12 [2H, m, H(2') + H(6')], 8.42-8.59 [2H, m, H(3') + H(5')].

*Sample contained impurities including triphenylphosphine oxide from previous reaction.

2-(Piperidin-4-ylmethyl)pyridine (34a)

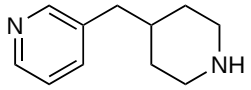


Using General Method 4, **76a** (330 mg, 1.19 mmol) in dichloromethane (12 mL) was reacted with trifluoroacetic acid (3.0 mL) for 1 hr. Work up afforded crude **34a** as an orange oil

which was used without further purification (90 mg, 43%*). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{11}H_{16}N_2$: 177.1392; found 177.1386. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.8$ Hz, $^3J_{(2/6)eq,(3/5)ax} = 3.6$ Hz, H(3_{ax}) + H(5_{ax})], 1.75 [2H, br d‡, $^2J_{(3/5)ax,(3/5)eq} = 12.8$ Hz, H(3_{eq}) + H(5_{eq})], 2.05 [1H, ttt, $^3J_{(3'/5')ax,4'ax} = 12.8$ Hz, $^3J_{4'ax,A} = 7.4$ Hz, $^3J_{(3'/5')eq,4'ax} = 3.5$ Hz, H($4'_{ax}$)], 2.65-2.84 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.26 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq} = 12.8$ Hz, H(2_{eq}) + H(6_{eq})], 4.83 [1H, br s, NH], 7.07-7.18 [2H, m, H(4') + H(6')], 7.60 [1H, br t‡, $^3J_{4',5'} = {}^3J_{5',6'} = 7.6$ Hz, H(5')], 8.54 [1H, br d‡, $^3J_{3',4'} = 4.7$ Hz, H(3')].

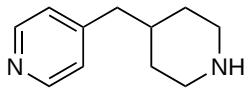
*Sample contained impurities including triphenylphosphine oxide from previous reaction.

3-(Piperidin-4-ylmethyl)pyridine (34b)



Using General Method 4, **76b** (32 mg, 0.12 mmol) in dichloromethane (5 mL) was reacted with trifluoroacetic acid (0.5 mL) for 1 hr. Work up did not yield any product.

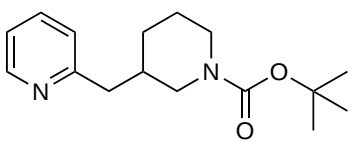
4-(Piperidin-4-ylmethyl)pyridine (34c)



Using General Method 4, **76c** (261 mg, 0.94 mmol) in dichloromethane (5 mL) was reacted with trifluoroacetic acid (2.0 mL) for 1 hr. Work up afforded crude **34c** as an orange oil which was used without further purification (101 mg, 61%*). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{11}H_{16}N_2$: 177.1392; found 177.1390. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.17 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.1$ Hz, $^3J_{(2/6)eq,(3/5)ax} = 3.5$ Hz, H(3_{ax}) + H(5_{ax})], 1.57-1.74 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.49-2.60 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.05 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq} = 12.3$ Hz, H(2_{eq}) + H(6_{eq})], 4.74 [1H, br s, NH], 7.03-7.13 [2H, m, H(2') + H(6')], 8.43-8.54 [2H, m, H(3') + H(5')].

*Sample contained impurities including triphenylphosphine oxide from previous reaction.

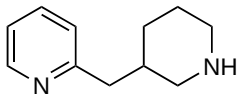
***tert*-Butyl 3-(pyridin-2-ylmethyl)piperidine-1-carboxylate (77a)**



Using General Method 3, **75a** (250 mg, 0.91 mmol) was reacted in methanol (30 mL) with Pd-C catalyst under a hydrogen atmosphere for 2 hr. Work-up and column chromatography

on silica gel eluting with 3:7 ethyl acetate/hexane gave **77a** as a yellow oil (251 mg, 100%). R_f = 0.19 (3:7 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{24}N_2O_2$: 277.1916; found 277.1915. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 [2H, qd, $^2J_{4ax,4eq} = {}^3J_{3,4ax} = {}^3J_{4ax,5ax} = 12.0$ Hz, $^3J_{4ax,5eq} = 3.8$ Hz, H(4_{ax})], 1.30-1.51 [11H, m, H(5_{ax}) + ^{t}Bu], 1.59-1.70 [1H, m, H(5_{eq})], 1.72-1.81 [1H, m, H(4_{eq})], 1.98 [1H, ttt, $^3J_{2ax,3} = {}^3J_{3,4ax} = 12.0$ Hz, $^3J_{3,A} = {}^3J_{3,A'} = 7.4$ Hz, H(3')], 2.49-2.69 [2H, m, H(2_{ax}) + H(A)], 2.72 [1H, dd, $^2J_{A,A'} = 13.5$ Hz, $^3J_{3,A'} = 7.4$ Hz, H(A')], 2.81 [1H, ddd, $^2J_{6ax,6eq} = 13.5$ Hz, $^3J_{5ax,6ax} = 10.7$ Hz, $^3J_{5eq,6ax} = 3.0$ Hz, H(6_{ax})], 3.68-4.07 [2H, m, H(2_{eq}) + H(6_{eq})], 7.08-7.16 [2H, m, H(4') + H(6')], 7.59 [1H, td, $^3J_{4',5'} = {}^3J_{5',6'} = 7.7$ Hz, $^4J_{3',5'} = 1.7$ Hz, H(5')], 8.54 [1H, br d‡, $^3J_{3',4'} = 4.0$ Hz, H(3')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.93 [br, C(5)], 28.54 [^{t}Bu], 30.91 [C(4)], 36.71 [C(3)], 42.49 [br, C(A)], 44.48 [br, C(6)], 49.89 [br, C(2)], 79.30 [^{t}Bu], 121.28 [C(4')], 123.60 [C(6')], 136.33 [C(5')], 149.46 [C(3')], 154.93 [C=O], 160.17 [C(1')].

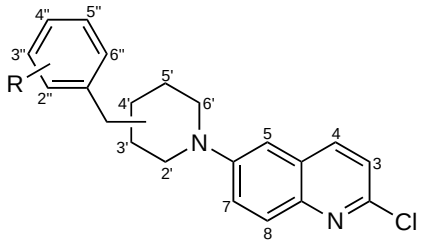
2-(Piperidin-3-ylmethyl)pyridine (35a)



Using General Method 4, **77a** (241 mg, 0.87 mmol) and trifluoroacetic acid (2 mL) were reacted in dichloromethane (8 mL) to give **35a** as a yellow oil (129 mg, 84%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{11}H_{16}N_2$: 177.1392; found 177.1391. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18-1.31 [1H, m, H(4_{ax})], 1.67-1.90 [3H, m, H(4_{eq}) + H(5_{ax}) + H(5_{eq})], 2.32 [1H, ttt, $^3J_{2ax,3ax} = {}^3J_{3ax,4ax} = 11.4$ Hz, $^3J_{3ax,A} = 7.4$ Hz, $^3J_{2eq,3ax} = {}^3J_{3ax,4eq} = 3.8$ Hz, H(3_{ax})], 2.60 [1H, dd, $^2J_{2ax,2eq} = 12.0$ Hz, $^3J_{2ax,3ax} = 11.4$ Hz, H(2_{ax})], 2.70-2.80 [3H, m, H(A) + H(6_{ax})], 3.20-3.28 [2H, m, H(2_{eq}) + H(6_{eq})], 4.74 [1H, br s, NH], 7.07-7.17 [2H, m, H(4') + H(6')], 7.61 [1H, td, $^3J_{4',5'} = {}^3J_{5',6'} = 7.6$ Hz, $^4J_{3',5'} = 1.8$ Hz, H(6')], 8.51 [1H, br d‡, $^3J_{3',4'} = 4.7$ Hz, H(3')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 22.83 [C(5)], 29.35 [C(4)], 34.71 [C(3)], 42.34 [C(A)], 44.65 [C(6)], 49.30 [C(2)], 121.74 [C(6)], 123.59 [C(4')], 136.70 [C(5')], 149.54 [C(3')], 158.68 [C(1')].

6.2.5 Synthesis of 2-chloroquinoline derivatives

General Method 9: Synthesis of 6-substituted 2-chloroquinolines via microwave-assisted Buchwald-Hartwig amination[52]

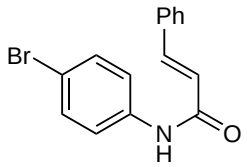


The benzylpiperidine derivative (1.0 eq) and 6-bromo-2-chloroquinoline (1.2 eq) were combined in a thick-walled glass pressure vessel with anhydrous (trifluoromethyl)benzene. To the flask was added $Pd(OAc)_2$ (0.5 mol %), CataCXium® A ligand (1 mol %) and sodium *tert*-butoxide (1.3 eq) and the vessel was purged with N_2 gas and sealed. The reaction mixture was heated at 150°C in a 300W Discover® Microwave System for the time specified, then cooled and filtered through Celite®, washing with methanol. The solvent was removed under reduced pressure and the mixture chromatographed on silica gel with the specified eluant.

General Method 10: Synthesis of 6-substituted 2-chloroquinolines via sealed-tube Buchwald-Hartwig amination[52]

The benzylpiperidine derivative (1.0 eq) and 6-bromo-2-chloroquinoline (1.2 eq) were combined in a glass pressure vessel with $Pd(OAc)_2$ (0.5 mol %), CataCXium® A ligand (1 mol %) and sodium *tert*-butoxide (1.3 eq). Anhydrous (trifluoromethyl)benzene (2 mL) was added and the vessel was purged with N_2 gas and sealed. The reaction mixture was heated at 110°C for 16 hr, then cooled and filtered through Celite® washing with methanol. The solvent was removed under reduced pressure and the mixture chromatographed on silica gel with the specified eluant.

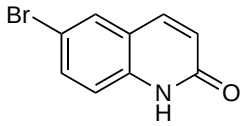
***N*-(4-Bromophenyl)cinnamamide (78)[76]**



A solution of cinnamoyl chloride (10.0 g, 60.0 mmol) in dichloromethane (20 mL) was added dropwise to a stirring solution of 4-(dimethylamino)pyridine (0.74 g, 6.0 mmol) and pyridine (4.8 mL, 60.0 mmol) in dichloromethane at 0°C under a nitrogen atmosphere. The mixture was stirred for 15 min. A solution of 4-bromoaniline (10.33 g, 60.0mmol) in dichloromethane

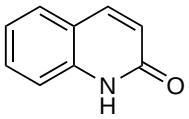
(20 mL) was added dropwise over 15 min and the mixture was stirred for 15 min at 0°C then 30 min at room temperature. The resultant precipitate was collected by vacuum filtration, washed with dichloromethane, and dried to give **78** as a pale purple solid (9.18 g, 51%). MP: 194-197°C (lit.[52] 193-195°) HRMS (ESI+) $[M+H]^+$ calcd. for $C_{15}H_{12}{}^{79}BrNO/C_{15}H_{12}{}^{81}BrNO$: 312.0181/304.0160; found 302.0169/304.0151. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.53 [1H, d, ^3J = 15.5 Hz, =CH], 7.31-7.60 [10H, m, Ar H's and NH], 7.76 [1H, d, ^3J = 15.5 Hz, =CH].

6-Bromoquinolin-2(1*H*)-one (79)[76]



Aluminium trichloride (11.9 g, 89.2 mmol) and **78** (9.0 g, 29.8 mmol) were ground together with a mortar and pestle until combined. The mixture was transferred to a round-bottom flask and heated to melting with a heat gun then at 110°C for 1.5 hr. The mixture was cooled to 0°C and quenched with ice-cold water. The precipitate was collected by vacuum filtration and washed with water to give a mixture of the desired product **79** and side-product quinolin-2(1*H*)-one (**179**) as a brown-pink solid which was used without further purification (6.04 g, <91%). Small samples of each product were isolated for characterisation.

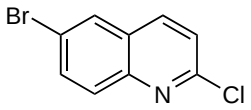
*6-Bromoquinolin-2(1*H*)-one (**79**):* HRMS (ESI+) $[M+H]^+$ calcd. for $C_9H_6{}^{79}BrNO/C_9H_6{}^{81}BrNO$: 223.9711/225.9691; found 223.9706/225.9686. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.75 [1H, d, $^3J_{3,4}$ = 9.5 Hz, H(3)], 7.31 [1H, d, $^3J_{7,8}$ = 8.8 Hz, H(8)], 7.61 [1H, d, $^3J_{7,8}$ = 8.8 Hz, H(7)], 7.69-7.80 [2H, m, H(4) + H(5)], 12.19 [1H, br s, NH].



179

*Quinolin-2(1*H*)-one (**179**):* HRMS (ESI+) $[M+H]^+$ calcd. for C_9H_7NO: 146.0606; found 146.0600. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 [1H, d, $^3J_{3,4}$ = 9.5 Hz, H(3)], 7.23 [1H, t, $^3J_{5,6}$ = $^3J_{6,7}$ = 7.8 Hz, H(6)], 7.45 [1H, d, $^3J_{7,8}$ = 7.8 Hz, H(8)], 7.52 [1H, t, $^3J_{6,7}$ = $^3J_{7,8}$ = 7.8 Hz, H(7)], 7.57 [1H, d, $^3J_{5,6}$ = 7.8 Hz, H(5)], 7.83 [1H, d, $^3J_{3,4}$ = 9.5 Hz, H(4)], 12.36 [1H, br s, NH].

6-Bromo-2-chloroquinoline (24)[76]

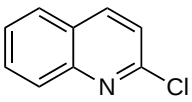


A mixture of **79** and **179** (7.60 g, <33.9 mmol of reagent **79***) was treated with phosphoryl chloride (32 mL, 0.34 mmol) and heated at reflux for 1 hr. The mixture was cooled to 0°C and slowly quenched with water. The precipitate was collected by vacuum filtration** and washed with ice water, then purified by flash column chromatography on silica gel eluting with 4:1 dichloromethane/hexane to give pure **24** as an off-white solid (2.63 g, >32%*). MP: 158-160°C (lit.[131] 157-158°C) HRMS (ESI+) $[M+H]^+$ calcd. for $C_9H_5{}^{79}Br{}^{35}ClN/C_9H_5{}^{81}Br{}^{35}ClN$: 241.9372/243.9352; found 241.9366/243.9345. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(3)], 7.81 [1H, dd, $^3J_{7,8}$ = 9.0 Hz, $^4J_{5,7}$ = 2.2 Hz, H(7)], 7.90 [1H, d, $^3J_{7,8}$ = 9.0 Hz, H(8)], 7.99 [1H, d, $^4J_{5,7}$ = 2.2 Hz, H(5)], 8.03 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(4)].

*Reagent **79** was not be purified and mixture contained a large amount of **179**. Minimum yield calculated assuming pure **79** used as reagent.

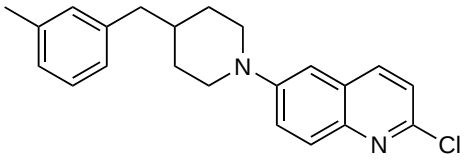
Slow crystallisation of the aqueous filtrate over 5 days yielded a crude sample of **24 and 2-chloroquinoline (**180**) as an off-white solid. HRMS (ESI+) $[M+H]^+$ calcd. for $C_9H_6{}^{35}ClN/C_9H_6{}^{37}ClN$: 164.0267/166.0238; found 164.0260/166.0232. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.44 [1H, m, H(3) + *H(3)], 7.57 [0.3H, ddd, $^3J_{*5,*6}$ = 8.1 Hz, $^3J_{*6,*7}$ = 7.0 Hz, $^4J_{*6,*8}$ = 1.1 Hz, *H(6)], 7.75 [0.3H, ddd, $^3J_{*7,*8}$ = 8.5 Hz, $^3J_{*6,*7}$ = 7.0 Hz, $^4J_{*5,*7}$ = 1.4 Hz, *H(7)], 7.78-7.85 [1H, m, H(7) + *H(5)], 7.90 [0.7H, d, $^3J_{7,8}$ = 9.0 Hz, H(8)], 7.99 [0.7H, d, $^4J_{5,7}$ = 2.2 Hz, H(5)], 8.00-8.05 [1H, m, H(4) + *H(8)], 8.11 [0.3H, d, $^3J_{*3,*4}$ = 8.6 Hz, *H(4)].

* denotes signals corresponding to minor product in isolated sample, **180**.



180

2-Chloro-6-(4-(3-methylbenzyl)piperidin-1-yl)quinoline (82c)



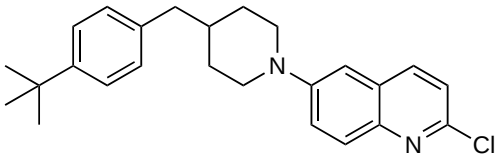
Synthesis method a. Using General Method 9, **31c** (43 mg, 0.22 mmol) and **24** (46 mg, 0.19 mmol) were combined in a thick-walled glass pressure vessel with (trifluoromethyl)benzene

(2 mL) and $Pd(OAc)_2$ (0.2 mg, 0.8 μmol), CataCXium® A ligand (0.8 mg, 2.2 μmol) and sodium *tert*-butoxide (22 mg, 0.22 mmol). The vessel was purged with N_2 gas and sealed. The reaction mixture was heated at 150°C in a 300W Discover® Microwave System for 20 min with 5 min ramp time. Work-up followed by column chromatography on silica gel eluting with 4:1 dichloromethane/hexane gave **82c** as a yellow oil (31 mg, 46%). R_f = 0.29 (4:1 dichloromethane/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq}$ = $^3J_{(2'/6')ax,(3'/5')ax}$ = $^3J_{(3'/5')ax,4'ax}$ = 12.4 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.4 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.66-1.92 [3H, m, H(3'$_{eq}$) + H(4'$_{ax}$) + H(5'$_{eq}$)], 2.35 [3H, s, CH_3], 2.56 [2H, d, $^3J_{4'ax,A}$ = 7.1 Hz, H(A)], 2.76 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq}$ = $^3J_{(2'/6')ax,(3'/5')ax}$ = 12.4 Hz, $^3J_{(2'/6')ax,(3'/5')eq}$ = 2.1 Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 3.80 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.4 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 6.94-7.06 [4H, m, H(5) + H(2") + H(4") + H(6")], 7.19 [1H, t, $^3J_{4",5"}$ = $^3J_{5",6"}$ = 7.6 Hz, H(5")], 7.25 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(3)], 7.48 [1H, dd, $^3J_{7,8}$ = 9.4 Hz, $^4J_{5,7}$ = 2.6 Hz, H(7)], 7.85 [1H, d, $^3J_{7,8}$ = 9.4 Hz, H(8)], 7.89 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.44 [CH_3], 31.86 [C(3') + C(5')], 37.84 [C(4')], 43.03 [C(A)], 49.65 [C(2') + C(6')], 108.74 [C(5)], 122.25 [C(3)], 123.60 [C(7)], 126.15 [*C(4") or C(5") or C(6")], 126.70 [*C(4") or C(5") or C(6")], 128.13 [*C(4") or C(5") or C(6")], 128.15 [C(4a)], 128.99 [C(8)], 129.92 [C(2")], 137.35 [C(4)], 137.82 [*C(1") or C(3")], 140.19 [*C(1") or C(3")], 142.87 [C(8a)], 147.15 [C(2)], 150.01 [C(6)].

*Interpretation of spectra and 2D NMR correlations could not achieve unambiguous assignment of all NMR signals due to overlapped signals in the ^{1}H NMR spectrum.

Synthesis method b. Using General Method 10, **31c** (50 mg, 0.26 mmol) and **24** (58 mg, 0.24 mmol) were reacted with $Pd(OAc)_2$ (0.3 mg, 1.3 μmol), CataCXium® A ligand (0.9 mg, 2.5 μmol) and sodium *tert*-butoxide (28 mg, 0.3 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **82c** as a yellow oil (79 mg, 85%). Data as above.

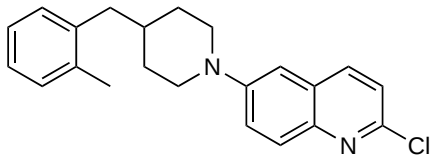
2-Chloro-6-(4-(4-*tert*-butylbenzyl)piperidin-1-yl)quinoline (82a)



Using General Method 10, **31a** (50 mg, 0.22 mmol) and **24** (43 mg, 0.18 mmol) were reacted with $Pd(OAc)_2$ (0.2 mg, 0.9 μmol), CataCXium® A ligand (0.8 mg, 2.2 μmol) and sodium *tert*-butoxide (24 mg, 0.25 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with 1:9 hexane/dichloromethane gave **82a** as a yellow oil (48 mg, 69%). R_f = 0.12 (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{25}H_{29}{}^{35}ClN_2$: 393.2098; found 393.2110. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32

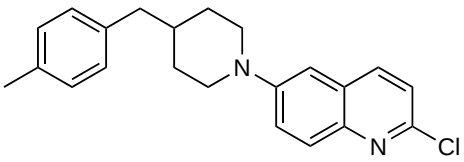
[9H, s, ^{t}Bu], 1.43 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.2$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 3.1$ Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.68-1.86 [3H, m, H(3'$_{eq}$) + H(4'$_{ax}$) + H(5'$_{eq}$)], 2.57 [2H, d, $^3J_{4'ax,A} = 7.0$ Hz, H(A)], 2.76 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = 12.2$ Hz, $^3J_{(2'/6')ax,(3'/5')eq} = 1.8$ Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 3.80 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.2$ Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 6.97 [1H, d, $^4J_{5,7} = 2.5$ Hz, H(5)], 7.07-7.14 [2H, m, H(2") + H(6")], 7.25 [1H, d, $^3J_{3,4} = 8.6$ Hz, H(3)], 7.29-7.35 [2H, m, H(3") + H(5")], 7.48 [1H, dd, $^3J_{7,8} = 9.3$ Hz, $^4J_{5,7} = 2.5$ Hz, H(7)], 7.84 [1H, d, $^3J_{7,8} = 9.3$ Hz, H(8)], 7.88 [1H, d, $^3J_{3,4} = 8.6$ Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.56 [^{t}Bu], 31.99 [C(3') + C(5')], 34.52 [^{t}Bu], 37.89 [C(4')], 42.67 [C(A)], 49.80 [C(2') + C(6')], 108.89 [C(5)], 122.39 [C(3)], 123.74 [C(7)], 125.27 [C(3") + C(5")], 128.29 [C(4a)], 128.92 [C(2") + C(6")], 129.13 [C(8)], 137.26 [C(1")], 137.49 [C(4)], 143.01 [C(8a)], 147.29 [C(2)], 148.91 [C(4")], 150.17 [C(6)].

2-Chloro-6-(4-(2-methylbenzyl)piperidin-1-yl)quinoline (82b)



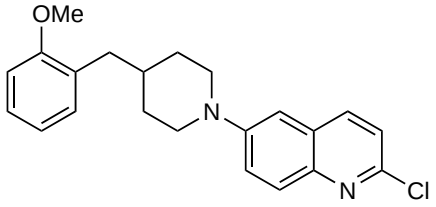
Using General Method 10, **31b** (69 mg, 0.36 mmol) and **24** (105 mg, 0.43 mmol) were reacted with $Pd(OAc)_2$ (0.4 mg, 1.8 μmol), CataCXium® A ligand (1.3 mg, 3.6 μmol) and sodium *tert*-butoxide (46 mg, 0.48 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **82a** as a yellow oil (30 mg, 23%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{23}{}^{35}ClN_2/C_{22}H_{23}{}^{37}ClN_2$: 351.1628/353.1599; found 351.1622/353.1599. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.2$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 3.4$ Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.67-1.88 [3H, m, H(3'$_{eq}$) + H(4'$_{ax}$) + H(5'$_{eq}$)], 2.33 [3H, s, CH_3], 2.61 [2H, d, $^3J_{4'ax,A} = 7.1$ Hz, H(A)], 2.76 [2H, t, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = 12.2$ Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 3.81 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.2$ Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 6.98 [1H, br s‡, H(5)], 7.07-7.21 [4H, m, H(3") + H(4") + H(5") + H(6")], 7.23-7.28 [1H, m, H(3)], 7.49 [1H, br d‡, $^3J_{7,8} = 9.3$ Hz, H(7)], 7.85 [1H, d, $^3J_{7,8} = 9.3$ Hz, H(8)], 7.90 [1H, d, $^3J_{3,4} = 8.7$ Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.71 [CH_3], 32.15 [C(3') + C(5')], 36.87 [C(4')], 40.31 [C(A)], 49.80 [C(2') + C(6')], 108.87 [C(5)], 122.36 [C(3)], 123.70 [C(7)], 125.78 [C(5")], 126.22 [C(4")], 128.26 [C(4a)], 129.10 [C(8)], 130.12 [C(6")], 130.43 [C(3")], 136.24 [C(2")], 137.47 [C(4)], 138.59 [C(1")], 142.98 [C(8a)], 147.26 [C(2)], 150.08 [C(6)].

2-Chloro-6-(4-(4-methylbenzyl)piperidin-1-yl)quinoline (82d)



Using General Method 10, **31d** (100 mg, 0.53 mmol) and **24** (153 mg, 0.63 mmol) were reacted with $Pd(OAc)_2$ (0.6 mg, 2.6 μmol), CataCXium® A ligand (1.9 mg, 6.8 μmol) and sodium *tert*-butoxide (66 mg, 0.69 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **82d** as a yellow oil (132 mg, 71%). R_f = 0.15 (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{23}{}^{35}ClN_2$: 351.1628; found 351.1627. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ = 12.3 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.9 Hz, $H(3'_{ax}) + H(5'_{ax})$], 1.71 [1H, ttt, $^3J_{(3'/5')ax,4'ax}$ = 12.3 Hz, $^3J_{4'ax,A}$ = 7.4 Hz, $^3J_{(3'/5')eq,4'ax}$ = 3.9 Hz, $H(4'_{ax})$], 1.80 [2H, br d‡, $^2J_{(3'/5')ax,(3'/5')eq}$ = 12.3 Hz, $H(3'_{eq}) + H(5'_{eq})$], 2.33 [3H, s, CH_3], 2.56 [2H, d, $^3J_{4'ax,A}$ = 7.4 Hz, H(A)], 2.76 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax}$ = 12.3 Hz, $^3J_{(2'/6')ax,(3'/5')eq}$ = 1.9 Hz, $H(2'_{ax}) + H(6'_{ax})$], 3.80 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.3 Hz, $H(2'_{eq}) + H(6'_{eq})$], 6.98 [1H, d, $^4J_{5,7}$ = 2.6 Hz, H(5)], 7.03-7.09 [2H, m, H(2") + H(6")], 7.09-7.15 [2H, m, H(3") + H(5")], 7.26 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(3)], 7.48 [1H, dd, $^3J_{7,8}$ = 9.3 Hz, $^4J_{5,7}$ = 2.6 Hz, H(7)], 7.85 [1H, d, $^3J_{7,8}$ = 9.3 Hz, H(8)], 7.89 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.17 [CH_3], 31.99 [C(3') + C(5')], 38.07 [C(4')], 42.79 [C(A)], 49.82 [C(2') + C(6')], 108.91 [C(5)], 122.41 [C(3)], 123.77 [C(7)], 128.30 [C(4a)], 129.11 [C(3") + C(5")], 129.15 [C(8)], 129.16 [C(2") + C(6")], 135.59 [C(4")], 137.29 [C(1")], 137.50 [C(4)], 143.04 [C(8a)], 147.31 [C(2)], 150.17 [C(6)].

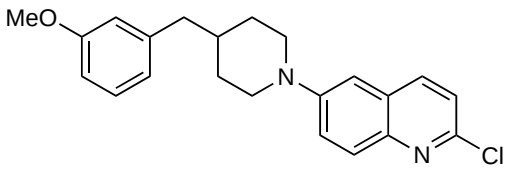
2-Chloro-6-(4-(2-methoxybenzyl)piperidin-1-yl)quinoline (82e)



Using General Method 10, **31e** (70 mg, 0.34 mmol) and **24** (99 mg, 0.41 mmol) were reacted with $Pd(OAc)_2$ (0.4 mg, 1.8 μmol), CataCXium® A ligand (1.2 mg, 3.3 μmol) and sodium *tert*-butoxide (43 mg, 0.45 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **82e** as a yellow oil (66 mg, 53%). R_f = 0.12 (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{23}{}^{35}ClN_2O/C_{22}H_{23}{}^{37}ClN_2O$: 367.1577/369.1548; found 367.1571/369.1551. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$

= 12.6 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.3 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.73-1.85 [3H, m, H($3'_{eq}$) + H($4'_{ax}$) + H($5'_{eq}$)], 2.61 [2H, d, $^{3}J_{4'ax,A}$ = 6.6 Hz, H(A)], 2.77 [2H, td, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = 12.6 Hz, $^{3}J_{(2'/6')ax,(3'/5')eq}$ = 2.1 Hz, H($2'_{ax}$) + H($6'_{ax}$)], 3.79 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.6 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 3.83 [3H, s, OCH_3], 6.85-6.92 [2H, m, H(3") + H(5")], 6.98 [1H, d, $^{4}J_{5,7}$ = 2.6 Hz, H(5)], 7.11 [1H, dd, $^{3}J_{5",6"}$ = 7.3 Hz, $^{4}J_{4",6"}$ = 1.7 Hz, H(6")], 7.21 [1H, td, $^{3}J_{3",4"}$ = $^{3}J_{4",5"}$ = 7.9 Hz, $^{4}J_{4",6"}$ = 1.7 Hz, H(4")], 7.25 [1H, d, $^{3}J_{3,4}$ = 8.6 Hz, H(3)], 7.49 [1H, dd, $^{3}J_{7,8}$ = 9.3 Hz, $^{4}J_{5,7}$ = 2.7 Hz, H(7)], 7.84 [1H, d, $^{3}J_{7,8}$ = 9.3 Hz, H(8)], 7.89 [1H, d, $^{3}J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.94 [C(3') + C(5')], 36.21 [C(A)], 37.13 [C(4')], 49.66 [C(2') + C(6')], 55.27 [OCH_3], 108.66 [C(5)], 110.36 [C(3")], 120.17 [C(5")], 122.23 [C(3)], 123.60 [C(7)], 127.24 [C(4")], 128.19 [C(4a)], 128.72 [C(1")], 128.96 [C(8)], 130.92 [C(6")], 137.35 [C(4)], 142.83 [C(8a)], 147.08 [C(2)], 150.08 [C(6)], 157.65 [C(2")].

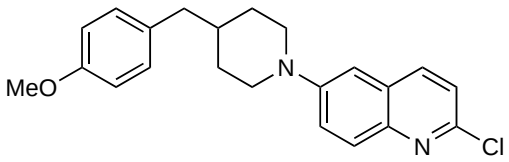
2-Chloro-6-(4-(3-methoxybenzyl)piperidin-1-yl)quinoline (82f)



Using General Method 10, **31f** (96 mg, 0.47 mmol) and **24** (102 mg, 0.42 mmol) were reacted with $Pd(OAc)_2$ (0.5 mg, 2.2 μmol), CataCXium® A ligand (1.5 mg, 4.2 μmol) and sodium *tert*-butoxide (49 mg, 0.51 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **82f** as a yellow oil (107 mg, 68%). R_f = 0.08 (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{23}{}^{35}ClN_2O$: 367.1577; found 367.1578. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 [2H, qd, $^{2}J_{(3'/5')ax,(3'/5')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = $^{3}J_{(3'/5')ax,4'ax}$ = 12.4 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.9 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.66-1.90 [3H, m, H($3'_{eq}$) + H($4'_{ax}$) + H($5'_{eq}$)], 2.57 [2H, d, $^{3}J_{4'ax,A}$ = 7.0 Hz, H(A)], 2.76 [2H, td, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = 12.4 Hz, $^{3}J_{(2'/6')ax,(3'/5')eq}$ = 1.4 Hz, H($2'_{ax}$) + H($6'_{ax}$)], 3.74-3.87 [5H, m, H($2'_{eq}$) + H($6'_{eq}$) + OCH_3], 6.68-6.83 [3H, m, H(2") + H(4") + H(6")], 6.97 [1H, d, $^{4}J_{5,7}$ = 2.3 Hz, H(5)], 7.17-7.28 [2H, m, H(3) + H(5")], 7.47 [1H, dd, $^{3}J_{7,8}$ = 9.3 Hz, $^{4}J_{5,7}$ = 2.3 Hz, H(7)], 7.84 [1H, d, $^{3}J_{7,8}$ = 9.3 Hz, H(8)], 7.89 [1H, d, $^{3}J_{3,4}$ = 8.7 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.84 [C(3') + C(5')], 37.75 [C(4')], 43.11 [C(A)], 49.63 [C(2') + C(6')], 55.15 [OCH_3], 108.78 [C(5)], 111.01 [*C(4")], 115.06 [*C(2")], 121.58 [*C(6")], 122.25 [C(3)], 123.60 [C(7)], 128.14 [C(4a)], 128.99 [C(8)], 129.21 [C(5")], 137.35 [C(4)], 141.89 [C(1")], 142.87 [C(8a)], 147.16 [C(2)], 149.98 [C(6)], 159.58 [C(3")].

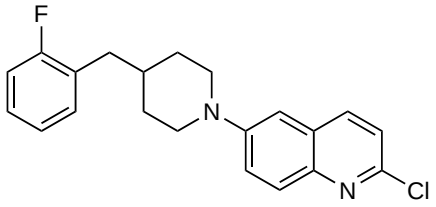
*Interpretation of spectra and 2D NMR correlations could not achieve unambiguous assignment of all NMR signals due to overlapped signals in the ^{1}H NMR spectrum.

2-Chloro-6-(4-(4-methoxybenzyl)piperidin-1-yl)quinoline (82g)



Using General Method 10, **31g** (50 mg, 0.24 mmol) and **24** (70 mg, 0.29 mmol) were reacted with $Pd(OAc)_2$ (0.3 mg, 1.3 μmol), CataCXium® A ligand (0.9 mg, 2.5 μmol) and sodium *tert*-butoxide (30 mg, 0.31 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **82g** as a yellow oil (50 mg, 56%). R_f = 0.20 (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{23}{}^{35}ClN_2O/C_{22}H_{23}{}^{37}ClN_2O$: 367.1577/369.1548; found 367.1571/369.1552. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ = 12.5 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.9 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.63-1.75 [1H, m, H(4')], 1.79 [2H, br d‡, $^2J_{(3'/5')ax,(3'/5')eq}$ = 12.5 Hz, H(3'$_{eq}$) + H(5'$_{eq}$)], 2.54 [2H, d, $^3J_{4'ax,A}$ = 7.1 Hz, H(A)], 2.76 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax}$ = 12.5 Hz, $^3J_{(2'/6')ax,(3'/5')eq}$ = 1.9 Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 3.77-3.83 [5H, m, H(2'$_{eq}$) + H(6'$_{eq}$) + OCH_3], 6.82-6.88 [2H, m, H(3'') + H(5'')], 6.98 [1H, d, $^4J_{5,7}$ = 2.6 Hz, H(5)], 7.06-7.12 [2H, m, H(2'') + H(6'')], 7.26 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(3)], 7.48 [1H, dd, $^3J_{7,8}$ = 9.4 Hz, $^4J_{5,7}$ = 2.6 Hz, H(7)], 7.85 [1H, d, $^3J_{7,8}$ = 9.4 Hz, H(8)], 7.90 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.79 [C(3') + C(5')], 38.02 [C(4')], 42.16 [C(A)], 49.67 [C(2') + C(6')], 55.26 [OCH_3], 108.77 [C(5)], 113.68 [C(3'') + C(5'')], 122.27 [C(3)], 123.63 [C(7)], 128.16 [C(4a)], 129.00 [C(8)], 130.00 [C(2'') + C(6'')], 132.30 [C(1'')], 137.36 [C(4)], 142.89 [C(8a)], 147.17 [C(2)], 150.02 [C(6)], 157.91 [C(4'')].

2-Chloro-6-(4-(2-fluorobenzyl)piperidin-1-yl)quinoline (82h)

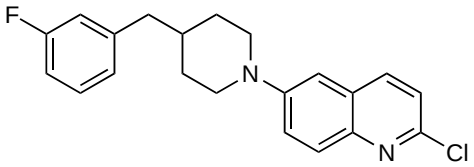


Using General Method 10, **31h** (56 mg, 0.29 mmol) and **24** (69 mg, 0.28 mmol) were reacted with $Pd(OAc)_2$ (0.3 mg, 1.3 μmol), CataCXium® A ligand (1.0 mg, 2.8 μmol) and sodium *tert*-butoxide (33 mg, 0.34 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave crude **82h** as a yellow oil which was used without further purification (67 mg, *70%). R_f = 0.17 (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{20}{}^{35}ClFN_2/C_{21}H_{20}{}^{37}ClFN_2$: 355.1377/357.1348; found 355.1375/357.1352. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 [2H, qd,

$^{2}J_{(3'/5')ax,(3'/5')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax} = {}^{3}J_{(3'/5')ax,4'ax} = 12.5$ Hz, $^{3}J_{(2'/6')eq,(3'/5')ax} = 2.9$ Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.73-1.84 [3H, m, H(3'$_{eq}$) + H(4'$_{ax}$) + H(5'$_{eq}$)], 2.65 [2H, d, $^{3}J_{4'ax,A} = 6.5$ Hz, H(A)], 2.77 [2H, br t‡, $^{2}J_{(2'/6')ax,(2'/6')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax} = 12.5$ Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 3.81 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq} = 12.5$ Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 6.98 [1H, d, $^{4}J_{5,7} = 2.5$ Hz, H(5)], 7.00-7.11 [2H, m, H(3") + H(5")], 7.14-7.23 [2H, m, H(4") + H(6")], 7.26 [1H, d, $^{3}J_{3,4} = 8.6$ Hz, H(3)], 7.48 [1H, dd, $^{3}J_{7,8} = 9.3$ Hz, $^{4}J_{5,7} = 2.5$ Hz, H(7)], 7.85 [1H, d, $^{3}J_{7,8} = 9.3$ Hz, H(8)], 7.90 [1H, d, $^{3}J_{3,4} = 8.6$ Hz, H(4)].

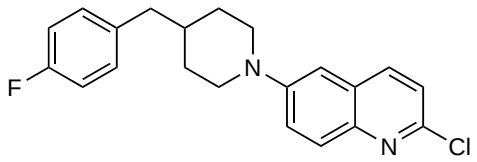
*Sample contained impurities including **31h**, which were not removed by column chromatography.

2-Chloro-6-(4-(3-fluorobenzyl)piperidin-1-yl)quinoline (82i)



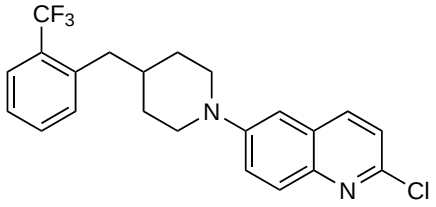
Using General Method 10, **31i** (162 mg, 0.84 mmol) and **24** (222 mg, 0.92 mmol) were reacted with $Pd(OAc)_2$ (0.9 mg, 4.0 μmol), CataCXium® A ligand (3.0 mg, 8.4 μmol) and sodium *tert*-butoxide (105 mg, 1.09 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **82i** as a yellow oil (168 mg, 56%). $R_f = 0.15$ (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 [2H, qd, $^{2}J_{(3'/5')ax,(3'/5')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax} = {}^{3}J_{(3'/5')ax,4'ax} = 12.5$ Hz, $^{3}J_{(2'/6')eq,(3'/5')ax} = 4.0$ Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.69-1.83 [3H, m, H(3'$_{eq}$) + H(4'$_{ax}$) + H(5'$_{eq}$)], 2.60 [2H, d, $^{3}J_{4'ax,A} = 7.0$ Hz, H(A)], 2.77 [2H, td, $^{2}J_{(2'/6')ax,(2'/6')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax} = 12.5$ Hz, $^{3}J_{(2'/6')ax,(3'/5')eq} = 2.4$ Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 3.81 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq} = 12.5$ Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 6.86-6.97 [3H, m, H(2") + H(4") + H(6")], 6.99 [1H, d, $^{4}J_{5,7} = 2.7$ Hz, H(5)], 7.23-7.29 [2H, m, H(3) + H(5")], 7.48 [1H, dd, $^{3}J_{7,8} = 9.3$ Hz, $^{4}J_{5,7} = 2.7$ Hz, H(7)], 7.85 [1H, d, $^{3}J_{7,8} = 9.3$ Hz, H(8)], 7.90 [1H, d, $^{3}J_{3,4} = 8.7$ Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.90 [C(3') + C(5')], 37.84 [C(4')], 42.94 [d, $^{4}J_{C,F} = 1.9$ Hz, C(A)], 49.77 [C(2') + C(6')], 109.00 [C(5)], 113.04 [d, $^{2}J_{C,F} = 21.0$ Hz, C(4")], 116.00 [d, $^{2}J_{C,F} = 20.5$ Hz, C(2")], 122.45 [C(3)], 123.77 [C(7)], 124.92 [d, $^{4}J_{C,F} = 2.9$ Hz, C(6")], 128.29 [C(4a)], 129.18 [C(8)], 129.81 [d, $^{3}J_{C,F} = 8.6$ Hz, C(5")], 137.52 [C(4)], 142.96 [d, $^{3}J_{C,F} = 7.2$ Hz, C(1")], 143.07 [C(8a)], 147.39 [C(2)], 150.08 [C(6)], 163.01 [d, $^{1}J_{C,F} = 245.6$ Hz, C(3")].

2-Chloro-6-(4-(4-fluorobenzyl)piperidin-1-yl)quinoline (82j)



Using General Method 10, **31j** (120 mg, 0.62 mmol) and **24** (180 mg, 0.74 mmol) were reacted with $Pd(OAc)_2$ (0.7 mg, 3.1 μmol), CataCXium® A ligand (2.2 mg, 6.1 μmol) and sodium *tert*-butoxide (78 mg, 0.81 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with 1:4 hexane/dichloromethane gave **82j** as a yellow oil (99 mg, 45%). $R_f = 0.58$ (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{20}{}^{35}ClFN_2/C_{21}H_{20}{}^{37}ClFN_2$: 355.1377/357.1348; found 355.1372/357.1350. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.2$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 3.6$ Hz, $H(3'_{ax}) + H(5'_{ax})$], 1.63-1.84 [3H, m, $H(3'_{eq}) + H(4'_{ax}) + H(5'_{eq})$], 2.56 [2H, d, $^3J_{4'ax,A} = 7.1$ Hz, C(A)], 2.75 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = 12.2$ Hz, $^3J_{(2'/6')ax,(3'/5')eq} = 2.1$ Hz, $H(2'_{ax}) + H(6'_{ax})$], 3.79 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.2$ Hz, $H(2'_{eq}) + H(6'_{eq})$], 6.95-7.02 [3H, m, H(5) + H(2") + H(6")], 7.08-7.15 [2H, m, H(3") + H(5")], 7.24 [1H, d, $^3J_{3,4} = 8.6$ Hz, H(3)], 7.47 [1H, dd, $^3J_{7,8} = 9.3$ Hz, $^4J_{5,7} = 2.7$ Hz, H(7)], 7.84 [1H, d, $^3J_{7,8} = 9.3$ Hz, H(8)], 7.88 [1H, d, $^3J_{3,4} = 8.6$ Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.83 [C(3') + C(5')], 38.02 [C(4')], 42.33 [br‡, C(A)], 49.72 [C(2') + C(6')], 108.93 [C(5)], 115.14 [d, $^2J_{C,F} = 21.0$ Hz, C(3") + C(5")], 122.39 [C(3)], 123.72 [C(7)], 128.26 [C(4a)], 129.11 [C(8)], 130.51 [d, $^3J_{C,F} = 7.6$ Hz, C(2") + C(6")], 135.93 [d, $^4J_{C,F} = 3.3$ Hz, C(1")], 137.48 [C(4)], 143.01 [C(8a)], 147.31 [C(2)], 150.06 [C(6)], 161.49 [d, $^1J_{C,F} = 243.7$ Hz, C(4")].

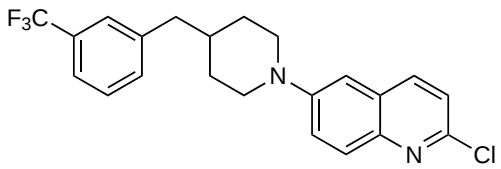
2-Chloro-6-(4-(2-(trifluoromethyl)benzyl)piperidin-1-yl)quinoline (82n)



Using General Method 10, **31n** (178 mg, 0.73 mmol) and **24** (194 mg, 0.80 mmol) were reacted with $Pd(OAc)_2$ (0.8 mg, 3.6 μmol), CataCXium® A ligand (2.6 mg, 7.3 μmol) and sodium *tert*-butoxide (91 mg, 0.95 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **82n** as a yellow oil (96 mg, 32%). $R_f = 0.33$ (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{20}{}^{35}ClF_3N_2/C_{22}H_{20}{}^{37}ClF_3N_2$: 405.1345/407.1316; found 405.1340/407.1319. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} =$

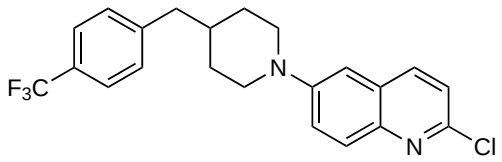
12.6 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.6 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.75-1.88 [3H, m, H(4') + H(3'$_{eq}$) + H(5'$_{eq}$)], 2.71-2.82 [4H, m, H(A) + H(2'$_{ax}$) + H(6'$_{ax}$)], 3.82 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.6 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 6.99 [1H, d, $^{4}J_{5,7}$ = 2.7 Hz, H(5)], 7.26 [1H, d, $^{3}J_{3,4}$ = 8.6 Hz, H(3)], 7.29-7.36 [2H, m, H(4') + H(6')], 7.45-7.52 [2H, m, H(7) + H(5')], 7.66 [1H, d, $^{3}J_{3',4'}$ = 7.6 Hz, H(3')], 7.85 [1H, d, $^{3}J_{7,8}$ = 9.3 Hz, H(8)], 7.90 [1H, d, $^{3}J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.93 [C(3') + C(5')], 37.49 [q, $^{4}J_{C,F}$ = 0.8 Hz, C(4')], 39.37 [q, $^{4}J_{C,F}$ = 1.4 Hz, C(A)], 49.70 [C(2') + C(6')], 108.86 [C(5)], 122.29 [C(3)], 123.64 [C(7)], 124.63 [q, $^{1}J_{C,F}$ = 273.8 Hz, CF_3], 126.19 [C(6'')], 126.23 [q, $^{3}J_{C,F}$ = 5.7 Hz, C(3'')], 128.14 [C(4a)], 128.89 [q, $^{2}J_{C,F}$ = 29.3 Hz, C(2'')], 129.03 [C(8)], 131.41 [q, $^{4}J_{C,F}$ = 0.8 Hz, C(4'')], 131.74 [C(5'')],137.39 [C(4)], 138.90 [q, $^{3}J_{C,F}$ = 1.8 Hz, C(1'')], 142.93 [C(8a)], 147.23 (C(2)), 149.94 [C(6)].

2-Chloro-6-(4-(3-(trifluoromethyl)benzyl)piperidin-1-yl)quinoline (82o)



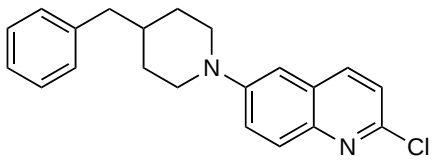
Using General Method 10, **31o** (58 mg, 0.24 mmol) and **24** (69 mg, 0.29 mmol) were reacted with $Pd(OAc)_2$ (0.3 mg, 1.2 μmol), CataCXium® A ligand (0.9 mg, 2.4 μmol) and sodium *tert*-butoxide (30 mg, 0.31 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **82o** as a yellow oil (49 mg, 51%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{20}{}^{35}ClF_3N_2/C_{22}H_{20}{}^{37}ClF_3N_2$: 405.1345/407.1316; found 405.1341/407.1321. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 [2H, qd, $^{2}J_{(3'/5')ax,(3'/5')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = $^{3}J_{(3'/5')ax,4'ax}$ = 12.0 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.1 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.70-1.84 [3H, m, H(4') + H(3'$_{eq}$) + H(5'$_{eq}$)], 2.67 [2H, d, $^{3}J_{4'ax,A}$ = 6.7 Hz, H(A)], 2.78 [2H, td, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = 12.0 Hz, $^{3}J_{(2'/6')ax,(3'/5')eq}$ = 1.8 Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 3.81 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.0 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 6.99 [1H, d, $^{4}J_{5,7}$ = 2.5 Hz, H(5)], 7.26 [1H, d, $^{3}J_{3,4}$ = 8.6 Hz, H(3)], 7.36 [1H, br d‡, $^{3}J_{5'',6''}$ = 7.6 Hz, H(6'')], 7.38-7.45 [2H, m, H(2'') + H(5'')], 7.45-7.52 [2H, m, H(7) + H(4'')], 7.85 [1H, d, $^{3}J_{7,8}$ = 9.3 Hz, H(8)], 7.90 [1H, d, $^{3}J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.85 [C(3') + C(5')], 37.89 [C(4')], 43.00 [C(A)], 49.73 [C(2') + C(6')], 109.03 [C(5)], 122.45 [C(3)], 123.10 [q, $^{3}J_{C,F}$ = 3.9 Hz, C(4'')], 123.76 [C(7)], 124.38 [q, $^{1}J_{C,F}$ = 272.3 Hz, CF_3], 125.83 [q, $^{3}J_{C,F}$ = 3.8 Hz, C(2'')], 128.28 [C(4a)], 128.85 [C(5'')], 129.20 [C(8)], 130.81 [q, $^{2}J_{C,F}$ = 32.0 Hz, C(3'')], 132.66 [br‡, C(6'')], 137.52 [C(4)], 141.25 [C(1'')], 143.09 [C(8a)], 147.42 [C(2)], 150.03 [C(6)].

2-Chloro-6-(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)quinoline (82p)



Using General Method 10, **31p** (131 mg, 0.54 mmol) and **24** (157 mg, 0.65 mmol) were reacted with $Pd(OAc)_2$ (0.6 mg, 2.7 μmol), CataCXium® A ligand (1.9 mg, 5.3 μmol) and sodium *tert*-butoxide (67 mg, 0.70 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **82p** as a yellow oil (136 mg, 62%). $R_f = 0.22$ (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.3$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 2.7$ Hz, $H(3'_{ax}) + H(5'_{ax})$], 1.70-1.83 [3H, m, $H(4') + H(3'_{eq}) + H(5'_{eq})$], 2.66 [2H, d, $^3J_{4'ax,A} = 6.7$ Hz, H(A)], 2.76 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = 12.3$ Hz, $^3J_{(2'/6')ax,(3'/5')eq} = 1.8$ Hz, $H(2'_{ax}) + H(6'_{ax})$], 3.80 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.3$ Hz, $H(2'_{eq}) + H(6'_{eq})$], 6.98 [1H, d, $^4J_{5,7} = 2.6$ Hz, H(5)], 7.25 [1H, d, $^3J_{3,4} = 8.6$ Hz, H(3)], 7.26-7.31 [2H, m, H(2") + H(6")], 7.47 [1H, dd, $^3J_{7,8} = 9.3$ Hz, $^4J_{5,7} = 2.6$ Hz, H(7)], 7.53-7.58 [2H, m, H(3") + H(5")], 7.85 [1H, d, $^3J_{7,8} = 9.3$ Hz, H(8)], 7.89 [1H, d, $^3J_{3,4} = 8.6$ Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.87 [C(3') + C(5')], 37.82 [C(4')], 42.99 [C(A)], 49.71 [C(2') + C(6')], 109.01 [C(5)], 122.43 [C(3)], 123.74 [C(7)], 124.47 [q, $^1J_{C,F} = 271.9$ Hz, CF_3], 125.35 [q, $^3J_{C,F} = 3.8$ Hz, C(3') + C(5')], 128.26 [C(4a)], 128.55 [q, $^2J_{C,F} = 32.3$ Hz, C(4')], 129.17 [C(8)], 129.52 [C(2') + C(6')], 137.51 [C(4)], 143.07 [C(8a)], 144.49 [q, $^5J_{C,F} = 1.4$ Hz, C(1')], 147.39 [C(2)], 150.02 [C(6)].

6-(4-Benzylpiperidin-1-yl)-2-chloroquinoline (82x)

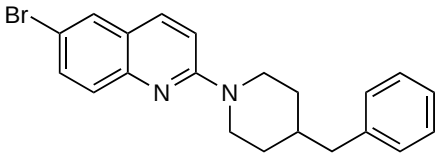


Synthesis method a. Using General Method 10, 4-benzylpiperidine (100 mg, 0.57 mmol) and **24** (137 mg, 0.56 mmol) were reacted with $Pd(OAc)_2$ (0.6 mg, 2.7 μmol), CataCXium® A ligand (2.0 mg, 5.6 μmol) and sodium *tert*-butoxide (66 mg, 0.69 mmol) in (trifluoromethyl)-benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **82x** as a yellow solid (143 mg, 75%). $R_f = 0.17$ (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.4$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 4.0$ Hz, $H(3'_{ax}) + H(5'_{ax})$], 1.68-1.85 [3H, m, $H(3'_{eq}) + H(4'_{ax}) + H(5'_{eq})$], 2.60 [2H, d, $^3J_{4'ax,A} = 7.0$ Hz, H(A)], 2.77 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = 12.4$ Hz, $^3J_{(2'/6')ax,(3'/5')eq} = 2.1$ Hz, $H(2'_{ax}) + H(6'_{ax})$], 3.80 [2H, br d‡,

$^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.4 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 6.98 [1H, d, $^{4}J_{5,7}$ = 2.6 Hz, H(5)], 7.13-7.19 [2H, m, H(2") + H(6")], 7.22 [1H, br t‡, $^{3}J_{3",4"} = {}^{3}J_{4",5"}$ = 7.3 Hz, H(4")], 7.26 [1H, d, $^{3}J_{3,4}$ = 8.6 Hz, H(3)], 7.27-7.34 [2H, m, H(3") + H(5")], 7.48 [1H, dd, $^{3}J_{7,8}$ = 9.3 Hz, $^{4}J_{5,7}$ = 2.6 Hz, H(7)], 7.85 [1H, d, $^{3}J_{7,8}$ = 9.3 Hz, H(8)], 7.89 [1H, d, $^{3}J_{3,4}$ = 8.6 Hz, H(4)].

This data is consistent with that reported in literature.[52]

Synthesis method b. 4-Benzylpiperidine (9.0 mg, 0.05 mmol) and **24** (15 mg, 0.06 mmol) were combined in a glass pressure tube with CataCXium® A ligand (0.2 mg, 0.5 μmol) and sodium *tert*-butoxide (6.4 mg, 0.07 mmol). (Trifluoromethyl)benzene (1.5 mL) was added and the vessel was purged with N_2 gas and sealed. The reaction mixture was heated at 110°C for 16 hr, then cooled and filtered through Celite® washing with methanol. The solvent was removed under reduced pressure and the mixture chromatographed on silica gel eluting with dichloromethane, to give **89x** as a white solid (11 mg, 64%).



89x

*2-(4-Benzylpiperidin-1-yl)-6-bromoquinoline (**89x**):* R_f = 0.44 (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{21}{}^{79}BrN_2/C_{21}H_{21}{}^{81}BrN_2$: 381.0966/383.0946; found 381.0964/383.0946. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 [2H, qd, $^{2}J_{(3'/5')ax,(3'/5')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax} = {}^{3}J_{(3'/5')ax,4'ax}$ = 12.2 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.7 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.73-1.89 [3H, m, H($3'_{eq}$) + H($4'_{ax}$) + H($5'_{eq}$)], 2.57 [2H, d, $^{3}J_{4'ax,A}$ = 7.4 Hz, H(A)], 2.89 [2H, td, $^{2}J_{(2'/6')ax,(2'/6')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax}$ = 12.2 Hz, $^{3}J_{(2'/6')ax,(3'/5')eq}$ = 1.9 Hz, H($2'_{ax}$) + H($6'_{ax}$)], 4.52 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.2 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 6.97 [1H, d, $^{3}J_{3,4}$ = 9.2 Hz, H(3)], 7.14-7.18 [2H, m, H(2") + H(6")], 7.21 [1H, t, $^{3}J_{3",4"} = {}^{3}J_{4",5"}$ = 7.5 Hz, H(4")], 7.26-7.32 [2H, m, H(3") + H(5")], 7.52 [1H, d, $^{3}J_{7,8}$ = 8.9 Hz, H(8)], 7.55 [1H, dd, $^{3}J_{7,8}$ = 8.9 Hz, $^{4}J_{5,7}$ = 1.9 Hz, H(7)], 7.69 [1H, d, $^{4}J_{5,7}$ = 1.9 Hz, H(5)], 7.74 [1H, d, $^{3}J_{3,4}$ = 9.2 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.14 [C(3') + C(5')], 38.63 [C(4')], 43.36 [C(A)], 45.63 [C(2') + C(6')], 110.70 [C(3)], 114.82 [C(6)], 124.10 [C(4a)], 126.12 [C(4")], 128.39 [C(8)], 128.42 [C(3") + C(5")], 129.25 [C(5)], 129.30 [C(2") + C(6")], 132.64 [C(7)], 136.39 [C(4)], 140.45 [C(1")], 147.00 [C(8a)], 157.56 [C(2)].

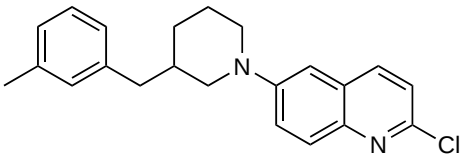
Synthesis method c. 4-Benzylpiperidine (50 mg, 0.29 mmol) and **24** (83 mg, 0.34 mmol) were combined in a glass pressure tube with $Pd(OAc)_2$ (0.3 mg, 1.4 μmol), CataCXium® A ligand (1.0 mg, 2.9 μmol) and sodium *tert*-butoxide (36 mg, 0.37 mmol). 1,4-Dioxane (2 mL) was added and the vessel was purged with N_2 gas and sealed. The reaction mixture was heated at 100°C for 16 hr, then cooled and filtered through Celite® washing with methanol. The solvent was removed under reduced pressure to give a crude residue which could not be

purified. ^{1}H NMR analysis indicated that the mixture contained a 5:1 ratio of **82x** and **27x**, when compared to data above.

Synthesis method d. 4-Benzylpiperidine (50 mg, 0.29 mmol) and **24** (83 mg, 0.34 mmol) were combined in a glass pressure tube with $Pd(OAc)_2$ (0.3 mg, 1.4 μmol), JohnPhos ligand (0.9 mg, 2.9 μmol) and sodium *tert*-butoxide (36 mg, 0.37 mmol). 1,4-Dioxane (2 mL) was added and the vessel was purged with N_2 gas and sealed. The reaction mixture was heated at 100°C for 16 hr, then cooled and filtered through Celite® washing with methanol. The solvent was removed under reduced pressure to give a crude residue which was not purified. ^{1}H NMR analysis determined that the mixture contained a 2:3 ratio of **82x** and **27x**, compared to data above.

Synthesis method e. 4-Benzylpiperidine (50 mg, 0.29 mmol) and **24** (83 mg, 0.34 mmol) were combined in a glass pressure tube with $Pd(OAc)_2$ (0.3 mg, 1.4 μmol), CyJohnPhos ligand (1.0 mg, 2.9 μmol) and sodium *tert*-butoxide (36 mg, 0.37 mmol). 1,4-Dioxane (2 mL) was added and the vessel was purged with N_2 gas and sealed. The reaction mixture was heated at 100°C for 16 hr, then cooled and filtered through Celite® washing with methanol. The solvent was removed under reduced pressure to give a crude residue which was not purified. ^{1}H NMR analysis determined that the mixture contained a 1:1 ratio of **82x** and **27x**, compared to data above.

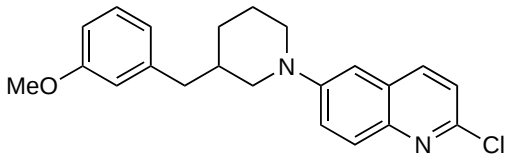
2-Chloro-6-(3-(3-methylbenzyl)piperidin-1-yl)quinoline (83c)



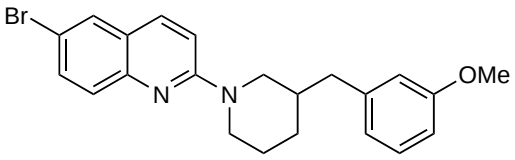
Using General Method 10, **32c** (100 mg, 0.53 mmol) and **24** (153 mg, 0.63 mmol) were reacted with $Pd(OAc)_2$ (0.6 mg, 2.7 μmol), CataCXium® A ligand (1.9 mg, 5.3 μmol) and sodium *tert*-butoxide (66 mg, 0.69 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with 4:1 dichloromethane/hexane gave **83c** as a yellow oil (78 mg, 42%). R_f = 0.60 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 [1H, qd, $^3J_{3'ax,4'ax} = {}^2J_{4'ax,4'eq} = {}^3J_{4'ax,5'ax}$ = 13.8 Hz, $^3J_{4'ax,5'eq}$ = 5.9 Hz, H(4'$_{ax}$)], 1.63-1.75 [1H, m, H(5'$_{ax}$)], 1.80-1.91 [2H, m, H(4'$_{eq}$) + H(5'$_{eq}$)], 1.97-2.08 [1H, m, H(3'$_{ax}$)], 2.36 [3H, s, CH_3], 2.55-2.67 [3H, m, H(2'$_{ax}$) + H(A)], 2.87 [1H, td, $^3J_{5'ax,6'ax} = {}^2J_{6'ax,6'eq}$ = 11.9 Hz, $^3J_{5'eq,6'ax}$ = 2.6 Hz, H(6'$_{ax}$)], 3.67 [1H, br d‡, $^2J_{2'ax,2'eq}$ = 12.2 Hz, H(2'$_{eq}$)], 3.72 [1H, br d‡, $^2J_{6'ax,6'eq}$ = 12.4 Hz, H(6'$_{eq}$)], 6.92 [1H, d, $^4J_{5,7}$ = 2.6 Hz, H(5)], 7.01 [1H, d, $^3J_{4'',5''}$ = 7.6 Hz, H(4'')], 7.03 [1H, s, H(2'')], 7.06 [1H, d, $^3J_{5'',6''}$ = 7.6 Hz, H(6'')], 7.22 [1H, t, $^3J_{4'',5''} = {}^3J_{5'',6''}$ = 7.5 Hz, H(5'')], 7.26 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(3)], 7.42 [1H, dd, $^3J_{7,8}$ = 9.3 Hz, $^4J_{5,7}$ = 2.7 Hz, H(7)], 7.83 [1H, d, $^3J_{7,8}$ = 9.3 Hz, H(8)], 7.87

[1H, d, $^3J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.44 [CH_3], 24.82 [C(5')], 36.73 [C(4')], 37.44 [C(3')], 40.52 [C(A)], 50.03 [C(6')], 55.37 [C(2')], 108.65 [C(5)], 122.23 [C(3)], 123.53 [C(7)], 126.04 [C(4'')], 126.84 [C(6'')], 128.16 [C(4a)], 128.25 [C(5'')], 128.96 [C(8)], 129.81 [C(2'')], 137.31 [C(4)], 137.93 [C(3'')], 139.91 [C(1'')], 142.78 [C(8a)], 147.07 [C(2)], 150.00 [C(6)].

2-Chloro-6-(3-(3-methoxybenzyl)piperidin-1-yl)quinoline (83f)



Using General Method 10, **32f** (60 mg, 0.29 mmol) and **24** (85 mg, 0.35 mmol) were reacted with $Pd(OAc)_2$ (0.3 mg, 1.3 μmol), CataCXium® A ligand (1.0 mg, 2.8 μmol) and sodium *tert*-butoxide (37 mg, 0.39 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with 4:1 dichloromethane/hexane yielded only **87f** as a yellow oil (21 mg, 17%).

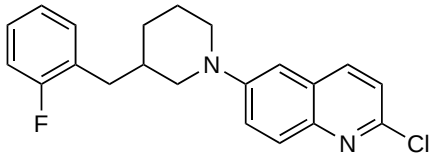


87f

*6-Bromo-2-(3-(3-methoxybenzyl)piperidin-1-yl)quinoline (**87f**):* R_f = 0.43 (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{23}{}^{79}BrN_2O/C_{22}H_{23}{}^{81}BrN_2O$: 411.1072/413.1052; found 411.1066/413.1048. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 [1H, br qd‡, $^2J_{4'ax,4'eq}$ = $^3J_{3'ax,4'ax}$ = $^3J_{4'ax,5'ax}$ = 12.0 Hz, $^3J_{4'ax,5'eq}$ = 3.9 Hz, H($4'_{ax}$)], 1.55 [1H, qt, $^2J_{5'ax,5'eq}$ = $^3J_{4'ax,5'ax}$ = $^3J_{5'ax,6'ax}$ = 12.0 Hz, $^3J_{4'eq,5'ax}$ = $^3J_{5'ax,6'eq}$ = 3.9 Hz, H($5'_{ax}$)], 1.74-1.97 [3H, m, H($3'_{ax}$) + H($4'_{eq}$) + H($5'_{eq}$)], 2.54 and 2.66 [2H, *ABX*, *A*:dd, *B*:dd, $^2J_{A,A'}(J_{AB})$ = 13.6 Hz, $^3J_{A,3'ax}(J_{AX})$ = 7.5 Hz, $^3J_{A',3'ax}(J_{BX})$ = 7.1 Hz, H(A) + H(A')], 2.77 [1H, dd, $^2J_{2'ax,2'eq}$ = 13.0 Hz, $^3J_{2'ax,3'ax}$ = 10.2 Hz, H($2'_{ax}$)], 3.05 [1H, ddd, $^2J_{6'ax,6'eq}$ = 13.1 Hz, $^3J_{5'ax,6'ax}$ = 12.0 Hz, $^3J_{5'eq,6'ax}$ = 3.0 Hz, H($6'_{ax}$)], 3.80 [3H, s, OCH_3], 4.29-4.42 [2H m, H($2'_{eq}$) + H($6'_{eq}$)], 6.73-6.82 [3H, m, H(2'') + H(4'') + H(6'')], 6.87 [1H, d, $^3J_{3,4}$ = 9.2 Hz, H(3)], 7.23 [1H, t, $^3J_{4',5'}$ = $^3J_{5',6'}$ = 7.8 Hz, H(5'')], 7.51 and 7.55 [2H, *ABX*, *A*:d, *B*:dd, $^3J_{7,8}(J_{AB})$ = 8.9 Hz, $^4J_{5,7}(J_{BX})$ = 2.1 Hz, H(8) + H(7)], 7.68 [1H, d, $^4J_{5,7}$ = 2.1 Hz, H(5)], 7.71 [1H, d, $^3J_{3,4}$ = 9.2 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.07 [C(5')], 31.25 [C(4')], 37.67 [C(3')], 40.60 [C(A)], 46.05 [C(6')], 51.29 [C(2')], 55.31 [OCH_3], 110.65 [C(3)], 111.45 [C(4'')], 114.77 [C(6)], 114.96 [C(2'')], 121.64 [C(6'')], 124.06 [C(4a)], 128.37 [C(8)], 129.22 [C(5)], 129.41

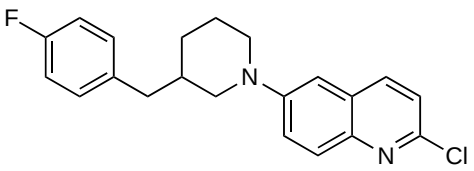
[C(5")], 132.60 [C(7)], 136.35 [C(4)], 141.80 [C(1")], 146.96 [C(8a)], 157.54 [C(2)], 159.78 [C(3")].

2-Chloro-6-(3-(2-fluorobenzyl)piperidin-1-yl)quinoline (83h)



Using General Method 10, **32h** (20 mg, 0.10 mmol) and **24** (30 mg, 0.13 mmol) were reacted with $Pd(OAc)_2$ (0.1 mg, 0.5 μmol), CataCXium® A ligand (0.4 mg, 1.0 μmol) and sodium *tert*-butoxide (13 mg, 0.14 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **83h** as a yellow oil (16 mg, 54%). R_f = 0.29 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 [1H, qd, $^3J_{3'ax,4'ax} = {}^2J_{4'ax,4'eq} = {}^3J_{4'ax,5'ax}$ = 12.0 Hz, $^3J_{4'ax,5'eq}$ = 4.0 Hz, H(4'$_{ax}$)], 1.68 [1H, qt, $^3J_{4'ax,5'ax} = {}^2J_{5'ax,5'eq} = {}^3J_{5'ax,6'ax}$ = 12.0 Hz, $^3J_{4'eq,5'ax} = {}^3J_{5'ax,6'eq}$ = 4.0 Hz, H(5'$_{ax}$)], 1.79-1.91 [2H, m, H(4'$_{eq}$) + H(5'$_{eq}$)], 2.05 [1H, ttt, $^3J_{2'ax,3'ax} = {}^3J_{3'ax,4'ax}$ = 12.0 Hz, $^3J_{A,3'ax} = {}^3J_{A',3'ax}$ = 7.8 Hz, $^3J_{2'eq,3'ax} = {}^3J_{3'ax,4'eq}$ = 4.0 Hz, H(3'$_{ax}$)], 2.58-2.74 [3H, m, H(2'$_{ax}$) + H(A) + H(A')], 2.84 [1H, td, $^3J_{5'ax,6'ax} = {}^2J_{6'ax,6'eq}$ = 12.0 Hz, $^3J_{5'eq,6'ax}$ = 2.9 Hz, H(6'$_{ax}$)], 3.63-3.75 [2H, m, H(2'$_{eq}$) + H(6'$_{eq}$)], 6.93 [1H, d, $^4J_{5,7}$ = 2.7 Hz, H(5)], 7.02-7.13 [2H, m, H(3") + H(5")], 7.16-7.28 [3H, m, H(3) + H(4") + H(6")], 7.42 [1H, dd, $^3J_{7,8}$ = 9.3 Hz, $^4J_{5,7}$ = 2.7 Hz, H(7)], 7.83 [1H, d, $^3J_{7,8}$ = 9.3 Hz, H(8)], 7.87 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.99 [C(5')], 30.68 [C(4')], 33.68 [d, $^3J_{C,F}$ = 1.9 Hz, C(A)], 36.78 [C(3')], 50.24 [C(6')], 55.49 [C(2')], 108.94 [C(5)], 115.50 [d, $^2J_{C,F}$ = 22.9 Hz, C(3")], 122.40 [C(3)], 123.78 [C(7)], 124.09 [d, $^4J_{C,F}$ = 3.3 Hz, C(5")], 127.01 [d, $^2J_{C,F}$ = 16.2 Hz, C(1")], 128.07 [d, $^3J_{C,F}$ = 8.1 Hz, C(4")], 128.28 [C(4a)], 129.15 [C(8)], 131.48 [d, $^3J_{C,F}$ = 5.2 Hz, C(6")], 137.51 [C(4)], 143.01 [C(8a)], 147.31 [C(2)], 150.19 [C(6)], 161.42 [d, $^1J_{C,F}$ = 244.6 Hz, C(2")].

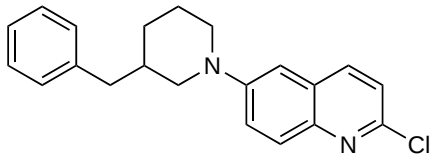
2-Chloro-6-(3-(4-fluorobenzyl)piperidin-1-yl)quinoline (83j)



Using General Method 10, **32j** (181 mg, 0.94 mmol) and **24** (274 mg, 1.13 mmol) were reacted with $Pd(OAc)_2$ (1.1 mg, 4.7 μmol), CataCXium® A ligand (3.4 mg, 9.4 μmol) and sodium *tert*-butoxide (117 mg, 1.22 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **83j**

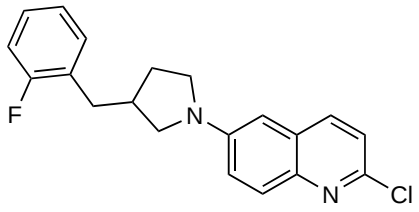
as a yellow oil (120 mg, 36%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13-1.27 [1H, m, H(4'$_{ax}$)], 1.63-1.74 [1H, m, H(5'$_{ax}$)], 1.79-1.90 [2H, m, H(4'$_{eq}$) + H(5'$_{eq}$)], 1.98 [1H, ttt, $^{3}J_{2'ax,3'ax}$ = $^{3}J_{3'ax,4'ax}$ = 12.0 Hz, $^{3}J_{A,3'ax}$ = $^{3}J_{A',3'ax}$ = 7.8 Hz, $^{3}J_{2'eq,3'ax}$ = $^{3}J_{3'ax,4'eq}$ = 3.8 Hz, H(3'$_{ax}$)], 2.53-2.66 [3H, m, H(2'$_{ax}$) + H(A) + H(A')], 2.85 [1H, td, $^{3}J_{5'ax,6'ax}$ = $^{2}J_{6'ax,6'eq}$ = 12.0 Hz, $^{3}J_{5'eq,6'ax}$ = 2.5 Hz, H(6'$_{ax}$)], 3.64 [1H, dd, $^{2}J_{6'ax,6'eq}$ = 12.0 Hz, $^{3}J_{5'ax,6'eq}$ = 2.1 Hz, H(6'$_{eq}$)], 3.70 [1H, br d‡, $^{2}J_{2'ax,2'eq}$ = 12.0 Hz, H(2'$_{eq}$)], 6.91 [1H, d, $^{4}J_{5,7}$ = 2.6 Hz, H(5)], 6.97-7.04 [2H, m, H(3") + H(5")], 7.11-7.17 [2H, m, H(2") + H(6")], 7.25 [1H, d, $^{3}J_{3,4}$ = 8.6 Hz, H(3)], 7.40 [1H, dd, $^{3}J_{7,8}$ = 9.3 Hz, $^{4}J_{5,7}$ = 2.6 Hz, H(7)], 7.83 [1H, d, $^{3}J_{7,8}$ = 9.3 Hz, H(8)], 7.87 [1H, d, $^{3}J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.95 [C(5')], 30.70 [C(4')], 37.79 [C(A)], 39.91 [C(3')], 50.21 [C(6')], 55.47 [C(2')], 108.90 [C(5)], 115.31 [d, $^{2}J_{C,F}$ = 21.0 Hz, C(3") + C(5")], 122.43 [C(3)], 123.71 [C(7)], 128.28 [C(4a)], 129.17 [C(8)], 130.44 [d, $^{3}J_{C,F}$ = 7.6 Hz, C(2") + C(6")], 135.70 [d, $^{4}J_{C,F}$ = 3.3 Hz, C(1")], 137.48 [C(4)], 143.00 [C(8a)], 147.33 [C(2)], 150.14 [C(6)], 161.58 [d, $^{1}J_{C,F}$ = 243.7 Hz, C(2")].

6-(3-Benzylpiperidin-1-yl)-2-chloroquinoline (83x)



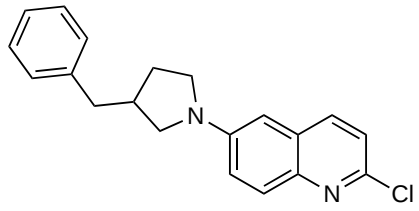
Using General Method 10, **32x** (171 mg, 0.98 mmol) and **24** (284 mg, 1.17 mmol) were reacted with $Pd(OAc)_2$ (1.1 mg, 4.9 μmol), CataCXium® A ligand (3.5 mg, 9.8 μmol) and sodium *tert*-butoxide (122 mg, 1.27 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with 1:9 hexane/dichloromethane gave **83x** as a yellow oil (104 mg, 32%). R_f = 0.20 (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{21}{}^{35}ClN_2/C_{21}H_{21}{}^{37}ClN_2$: 337.1472/339.1442; found 337.1465/339.1445. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21 [1H, qd, $^{3}J_{3'ax,4'ax}$ = $^{2}J_{4'ax,4'eq}$ = $^{3}J_{4'ax,5'ax}$ = 12.2 Hz, $^{3}J_{4'ax,5'eq}$ = 4.9 Hz, H(4'$_{ax}$)], 1.68 [1H, qt, $^{3}J_{4'ax,5'ax}$ = $^{2}J_{5'ax,5'eq}$ = $^{3}J_{5'ax,6'ax}$ = 12.2 Hz, $^{3}J_{4'eq,5'ax}$ = $^{3}J_{5'ax,6'eq}$ = 3.8 Hz, H(5'$_{ax}$)], 1.78-1.90 [2H, m, H(4'$_{eq}$) + H(5'$_{eq}$)], 1.96-2.08 [1H, m, H(3'$_{ax}$)], 2.56-2.68 [3H, m, H(2'$_{ax}$) + H(A) + H(A')], 2.85 [1H, td, $^{3}J_{5'ax,6'ax}$ = $^{2}J_{6'ax,6'eq}$ = 12.2 Hz, $^{3}J_{5'eq,6'ax}$ = 2.3 Hz, H(6'$_{ax}$)], 3.66 [1H, dd, $^{2}J_{2'ax,2'eq}$ = 12.1 Hz, $^{3}J_{2'eq,3'ax}$ = 1.5 Hz, H(2'$_{eq}$)], 3.71 [1H, dt, $^{2}J_{6'ax,6'eq}$ = 12.2 Hz, $^{4}J_{4'eq,6'eq}$ = $^{3}J_{5'ax,6'eq}$ = 3.8 Hz, H(6'$_{eq}$)], 6.90 [1H, d, $^{4}J_{5,7}$ = 2.3 Hz, H(5)], 7.16-7.28 [4H, m, H(2") + H(3) + H(4") + H(6")], 7.28-7.36 [2H, m, H(3") + H(5")], 7.41 [1H, dd, $^{3}J_{7,8}$ = 9.4 Hz, $^{4}J_{5,7}$ = 2.3 Hz, H(7)], 7.82 [1H, d, $^{3}J_{7,8}$ = 9.4 Hz, H(8)], 7.86 [1H, d, $^{3}J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.00 [C(5')], 30.85 [C(4')], 37.67 [C(3')], 40.79 [C(A)], 39.91 [C(3')], 50.21 [C(6')], 55.53 [C(2')], 108.84 [C(5)], 122.39 [C(3)], 123.70 [C(7)], 126.27 [C(4")], 128.30 [C(4a)], 128.54 [C(3") + C(5")], 129.14 [C(8)], 129.17 [C(2") + C(6")], 137.48 [C(4)], 140.13 [C(1")], 142.96 [C(8a)], 147.26 [C(6)], 150.15 [C(2)].

2-Chloro-6-(3-(2-fluorobenzyl)pyrrolidin-1-yl)quinoline (84h)



Using General Method 10, **33h** (12 mg, 70.0 μmol) and **24** (19 mg, 78.4 μmol) were reacted with $Pd(OAc)_2$ (0.1 mg, 0.4 μmol), CataCXium® A ligand (0.3 mg, 0.8 μmol) and sodium *tert*-butoxide (8.0 mg, 0.083 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **84h** as a yellow oil (10 mg, 44%). R_f = 0.30 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.84 [1H, dq, $^2J_{4'a,4'b}$ = 12.2 Hz, $^3J_{3',4'a}$ = $^3J_{4'a,5'a}$ = 8.0 Hz, H(4'$_a$)], 2.17 [1H, dtd, $^2J_{4'a,4'b}$ = 12.2 Hz, $^3J_{3',4'b}$ = $^3J_{4'b,5'a}$ = 8.0 Hz, $^3J_{4'b,5'b}$ = 4.1 Hz, H(4'$_b$)], 2.70 [1H, septet, $^3J_{2'a,3'}$ = $^3J_{2'b,3'}$ = $^3J_{3',A}$ = $^3J_{3',A'}$ = $^3J_{3',4'a}$ = $^3J_{3',4'b}$ = 8.0 Hz, H(3')], 2.83 and 2.85 [2H, *ABX*, *A*:dd, *B*:dd, $^2J_{A,A'}(J_{AB})$ = 13.9 Hz, $^3J_{A,3'ax}(J_{AX})$ = 8.0 Hz, $^3J_{A',3'ax}(J_{BX})$ = 8.0 Hz, H(A) + H(A')], 3.14 [1H, dd, $^2J_{2'a,2'b}$ = 8.8 Hz, $^3J_{2'a,3'}$ = 8.0 Hz, H(2'$_a$)], 3.40 [1H, q, $^2J_{5'a,5'b}$ = $^3J_{4'a,5'a}$ = $^3J_{4'b,5'a}$ = 8.0 Hz, H(5'$_a$)], 3.46-3.56 [2H, m, H(2'$_b$) + H(5'$_b$)], 6.58 [1H, d, $^4J_{5,7}$ = 2.5 Hz, H(5)], 7.06 [1H, dd, $^3J_{3'',F}$ = 9.6 Hz, $^3J_{3'',4''}$ = 8.8 Hz, H(3'')], 7.10 [1H, t, $^3J_{4'',5''}$ = $^3J_{5'',6''}$ = 7.5 Hz, H(5'')], 7.15 [1H, dd, $^3J_{7,8}$ = 9.3 Hz, $^4J_{5,7}$ = 2.5 Hz, H(7)], 7.18-7.28 [3H, m, H(3) + H(4'') + H(6'')], 7.83 [1H, d, $^3J_{7,8}$ = 9.3 Hz, H(8)], 7.83 [1H, d, $^3J_{3,4}$ = 8.5 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.47 [C(4')], 32.89 [C(A)], 39.63 [C(3')], 47.61 [C(5')], 53.26 [C(2')], 103.43 [C(5)], 115.59 [d, $^2J_{C,F}$ = 22.3 Hz, C(3'')], 119.46 [C(7)], 122.41 [C(3)], 124.24 [d, $^4J_{C,F}$ = 3.5 Hz, C(5'')], 126.11 [d, $^2J_{C,F}$ = 14.6 Hz, C(1'')], 128.24 [d, $^3J_{C,F}$ = 8.2 Hz, C(4'')], 128.82 [C(4a)], 129.35 [C(8)], 131.17 [d, $^3J_{C,F}$ = 4.8 Hz, C(6'')], 136.73 [C(4)], 141.37 [C(8a)], 145.82 [C(2)], 146.22 [C(6)], 161.25 [d, $^1J_{C,F}$ = 224.0 Hz, C(2'')].

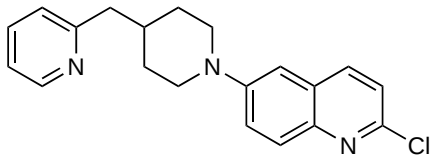
6-(3-Benzylpyrrolidin-1-yl)-2-chloroquinoline (84x)



Using General Method 10, **33x** (42 mg, 0.26 mmol) and **24** (76 mg, 0.32 mmol) were reacted with $Pd(OAc)_2$ (0.3 mg, 1.3 μmol), CataCXium® A ligand (0.9 mg, 2.5 μmol) and sodium *tert*-butoxide (33 mg, 0.34 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **84x** as a yellow oil (45 mg, 54%). R_f = 0.34 (dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.81 [1H,

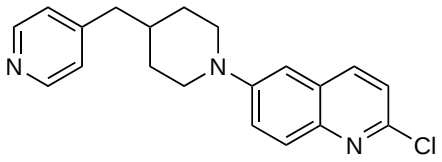
dq, $^{2}J_{4'a,4'b}$ = 12.3 Hz, $^{3}J_{3',4'a}$ = $^{3}J_{4'a,5'a}$ = $^{3}J_{4'a,5'b}$ = 8.4 Hz, H(4'a)], 2.13-2.21 [1H, m, H(4'b)], 2.66 [1H, pdd, $^{3}J_{3',4'a}$ = $^{3}J_{3',4'b}$ = $^{3}J_{3',4'a}$ = $^{3}J_{3',4'b}$ = 8.4 Hz, $^{3}J_{A,3'}$ = 7.7 Hz, $^{3}J_{A',3'}$ = 7.3 Hz, H(3')], 2.78 and 2.80 [2H, *ABX*, *A*:dd, *B*:dd, $^{2}J_{A,A'}(J_{AB})$ = 13.5 Hz, $^{3}J_{A,3'}(J_{AX})$ = 7.7 Hz, $^{3}J_{A',3'}(J_{BX})$ = 7.3 Hz, H(A) + H(A')], 3.11 [1H, t, $^{2}J_{2'a,2'b}$ = $^{3}J_{2'a,3'}$ = 8.4 Hz, H(2'a)], 3.38 [1H, q, $^{2}J_{5'a,5'b}$ = $^{3}J_{4'a,5'b}$ = $^{3}J_{4'b,5'b}$ = 8.4 Hz, H(5'a)], 3.44-3.54 [2H, m, H(2'b) + H(5'b)], 6.56 [1H, d, $^{4}J_{5,7}$ = 2.4 Hz, H(5)], 7.13 [1H, dd, $^{3}J_{7,8}$ = 9.2 Hz, $^{4}J_{5,7}$ = 2.4 Hz, H(7)], 7.18-7.25 [4H, m, H(3) + H(2'') + H(4'') + H(6'')], 7.29-7.35 [2H, m, H(3'') + H(5'')], 7.82 [1H, d, $^{3}J_{7,8}$ = 9.2 Hz, H(8)], 7.83 [1H, d, $^{3}J_{3,4}$ = 8.5 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.59 [C(4')], 39.88 [C(A)], 40.73 [C(3')], 47.64 [C(5')], 53.30 [C(2')], 103.39 [C(5)], 119.44 [C(7)], 122.38 [C(3)], 126.40 [C(4'')], 128.67 [C(3'') + C(5'')], 128.81 [C(4a)], 128.84 [C(2'') + C(6'')], 129.31 [C(8)], 136.71 [C(4)], 140.54 [C(1'')], 141.33 [C(8a)], 145.35 [C(2)], 146.21 [C(6)].

2-Chloro-6-(4-(pyridin-2-ylmethyl)piperidin-1-yl)quinoline (85a)



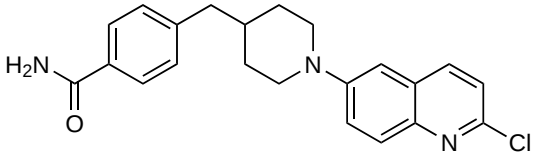
Using General Method 10, **34a** (80 mg, 0.45 mmol) and **24** (131 mg, 0.54 mmol) were reacted with $Pd(OAc)_2$ (0.5 mg, 2.2 μmol), CataCXium® A ligand (1.6 mg, 4.5 μmol) and sodium *tert*-butoxide (57 mg, 0.59 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with 5% methanol in dichloromethane gave **85a** as a yellow oil (74 mg, 48%). R_f = 0.57 (1:9 methanol/dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 [2H, qd, $^{2}J_{(3'/5')ax,(3'/5')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = $^{3}J_{(3'/5')ax,4'ax}$ = 12.6 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.8 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.80 [2H, br d‡, $^{2}J_{(3'/5')ax,(3'/5')eq}$ = 12.6 Hz, H($3'_{eq}$) + H($5'_{eq}$)], 1.97-2.10 [1H, m, H(4')], 2.74-2.84 [4H, m, H($2'_{ax}$) + H($6'_{ax}$) + H(A)], 3.80 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.4 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 6.98 [1H, d, $^{4}J_{5,7}$ = 2.2 Hz, H(5)], 7.10-7.17 [2H, m, H(4'') + H(6'')], 7.25 [1H, d, $^{3}J_{3,4}$ = 8.7 Hz, H(3)], 7.48 [1H, dd, $^{3}J_{7,8}$ = 9.3 Hz, $^{4}J_{5,7}$ = 2.2 Hz, H(7)], 7.61 [1H, t, $^{3}J_{4'',5''}$ = $^{3}J_{5'',6''}$ = 7.6 Hz, H(5'')], 7.85 [1H, d, $^{3}J_{7,8}$ = 9.3 Hz, H(8)], 7.90 [1H, d, $^{3}J_{3,4}$ = 8.7 Hz, H(4)], 8.57 [1H, br d‡, $^{3}J_{3'',4''}$ = 5.4 Hz, H(3'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.92 [C(3') + C(5')], 36.64 [C(4')], 45.31 [C(A)], 49.70 [C(2') + C(6')], 108.92 [C(5)], 121.28 [C(4'')], 122.35 [C(3)], 123.74 [C(7)], 123.79 [C(6'')], 128.24 [C(4a)], 129.08 [C(8)], 136.31 [C(5'')], 137.47 [C(4)], 142.99 [C(8a)], 147.26 [C(2)], 149.54 [C(3'')], 150.09 [C(6)], 160.37 [C(1'')].

2-Chloro-6-(4-(pyridin-4-ylmethyl)piperidin-1-yl)quinoline (28c)

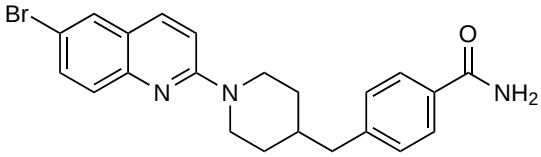


Using General Method 10, **34c** (97 mg, 0.55 mmol) and **24** (158 mg, 0.65 mmol) were reacted with $Pd(OAc)_2$ (0.6 mg, 2.7 μmol), CataCXium® A ligand (2.0 mg, 5.6 μmol) and sodium *tert*-butoxide (68 mg, 0.71 mmol) in (trifluoromethyl)benzene (2 mL). Reaction work-up gave a crude mixture containing only **24**; **34c** was not recovered.

4-((1-(2-Chloroquinolin-6-yl)piperidin-4-yl)methyl)benzamide (88)



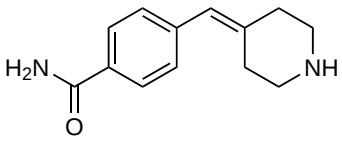
Synthesis method a. Using General Method 10, **65** (50 mg, 0.23 mmol) and **24** (67 mg, 0.28 mmol) were reacted with $Pd(OAc)_2$ (0.3 mg, 1.1 μmol), CataCXium® A ligand (0.8 mg, 2.3 μmol) and sodium *tert*-butoxide (29 mg, 0.30 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave an inseparable mixture which did not contain **88**. Signals indicating the presence of 4-((1-(6-bromoquinolin-2-yl)piperidin-4-yl)methyl)benzamide (**181**) were observed in the crude ^{1}H NMR spectrum.



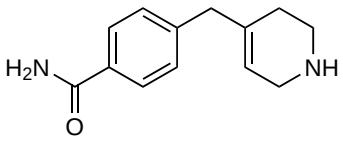
181

Synthesis method b. A mixture of **65** (125 mg, 0.57 mmol) and **24** (167 mg, 0.69 mmol) were combined with $Pd(OAc)_2$ (0.6 mg, 2.7 μmol), CataCXium® A ligand (2.1 mg, 5.9 μmol) and sodium *tert*-butoxide (72 mg, 0.75 mmol) in a glass pressure tube with 1,4-dioxane (2 mL). The flask was sealed and heated to 90°C for 16 hr, then cooled, diluted with methanol (5 mL), and filtered through Celite®, washing with methanol. The solvent was removed by evaporation under reduced pressure, and purification of the residue was attempted using column chromatography on silica gel eluting with dichloromethane to give a crude yellow oil (5 mg, 2%*). Characteristic signals corresponding to **181** were observed in ^{1}H NMR data. $R_f = 0.34$ (1% methanol in dichloromethane)

4-(Piperidin-4-ylidenemethyl)benzamide (90) and 4-((1,2,3,6-tetrahydropyridin-4-yl)methyl)benzamide (182)



90



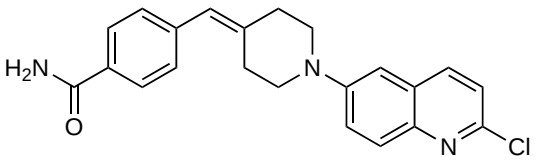
182

Using General Method 4, a mixture of **59** and **60** (302 mg, 0.99 mmol) was reacted with trifluoroacetic acid (3 mL) in dichloromethane (12 mL) for 1 hr, to give a mixture of **90** and **182** as a clear oil (30 mg, 14%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.92 [0.6H, br s‡, *H(5)], 2.31-2.39 [1.4H, m, H(5)], 2.41-2.50 [1.4H, m, H(3)], 2.82-2.91 [1.4H, m, H(2)], 2.93 [0.6H, t, $^{3}J_{*5,*6} = 5.7$ Hz, *H(6)], 2.95-3.03 [1.4H, m, H(6)], 3.30-3.39 [1.2H, m, *H(A) + *H(2)], 5.48 [0.3H, br s‡, *H(5)], 5.76-6.27 [3H, m, NH + $CONH_2$ + *NH + *$CONH_2$], 6.30 [0.7H, s, H(A)], 7.22-7.31 [2H, m, H(2') + H(6') + *H(2') + *H(6')], 7.70-7.80 [2H, m, H(3) + H(5) + *H(3) + *H(5)].

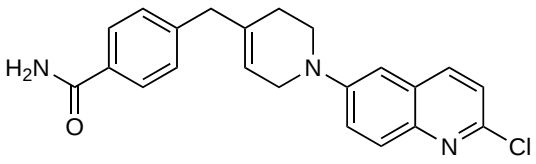
* denotes signals corresponding to the minor product **182**.

A small sample of almost pure **90** was isolated for the purposes of characterisation. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.31-2.39 [2H, m, H(5)], 2.41-2.50 [2H, m, H(3)], 2.82-2.91 [2H, m, H(2)], 2.95-3.03 [2H, m, H(6)], 5.66 [1H, br s, $CONH_2$], 6.05 [1H, br s, $CONH_2$], 6.31 [1H, s, H(A)], 7.21-7.31 [3H, m, NH + H(2') + H(6')], 7.73-7.79 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.08 [C(3)], 38.21 [C(5)], 47.76 [C(2)], 48.53 [C(6)], 122.62 [C(A)], 127.41 [C(3') + C(5')], 129.25 [C(2') + C(6')], 130.88 [C(4')], 141.90 [C(1')], 142.20 [C(4)], 169.14 [$CONH_2$].

4-((1-(2-Chloroquinolin-6-yl)piperidin-4-ylidene)methyl)benzamide (92) and 4-((1-(2-chloroquinolin-6-yl)-1,2,3,6-tetrahydropyridin-4-yl)methyl)benzamide (93)



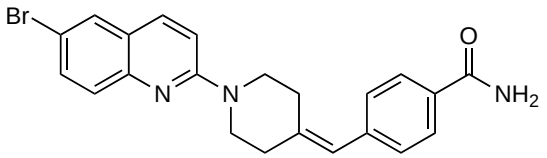
92



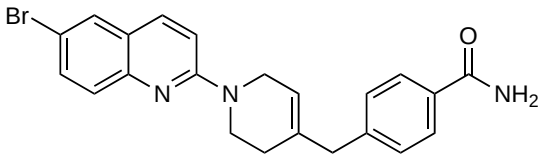
93

Using General Method 10, a mixture of **90** and **182** (20 mg, 0.09 mmol) and **24** (27 mg, 0.11 mmol) were reacted with $Pd(OAc)_2$ (1.0 mg, 0.5 μmol), CataCXium® A ligand (0.3 mg, 0.9 μmol) and sodium *tert*-butoxide (12 mg, 0.12 mmol) in (trifluoromethyl)benzene (2 mL). The volatile solvent was removed by evaporation under reduced pressure to give a crude residue. The mixture could not be separated using chromatographic methods, however ^{1}H NMR analysis of the crude mixture showed signals which may be consistent with the desired product

92, as well as 4-((1-(2-chloroquinolin-6-yl)-1,2,3,6-tetrahydropyridin-4-yl)methyl)benzamide (**93**), 4-((1-(6-bromoquinolin-2-yl)piperidin-4-ylidene)methyl)benzamide (**91**), 4-((1-(6-bromoquinolin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)methyl)benzamide (**94**), and recovered reagents.

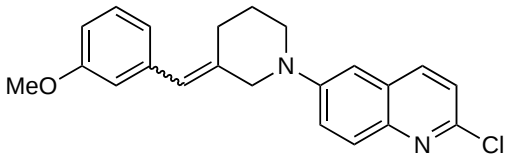


91

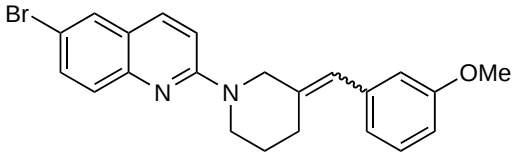


94

2-Chloro-6-(3-(3-methoxybenzylidene)piperidin-1-yl)quinoline (96f)

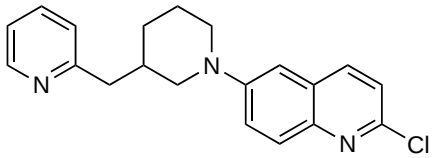


Using General Method 10, **95f** (42 mg, 0.21 mmol) and **24** (60 mg, 0.25 mmol) were reacted with $Pd(OAc)_2$ (0.2 mg, 1.0 μmol), CataCXium® A ligand (0.7 mg, 2.1 μmol) and sodium *tert*-butoxide (26 mg, 0.27 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave crude mixture which could not be purified. ^{1}H NMR analysis of the crude material indicated the mixture contained (*E*/*Z*)-**96f** and (*E*/*Z*)-6-bromo-2-(3-(3-methoxybenzylidene)piperidin-1-yl)quinoline (**97f**).



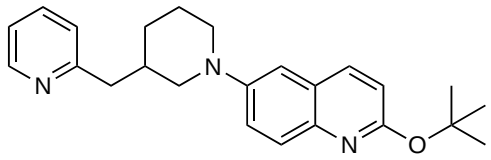
97f

2-Chloro-6-(3-(pyridin-2-ylmethyl)piperidin-1-yl)quinoline (98a)



Synthesis method a. Using General Method 10, **35a** (30 mg, 0.17 mmol) and **24** (49 mg, 0.20 mmol) were reacted with $Pd(OAc)_2$ (0.2 mg, 0.9 μmol), CataCXium® A ligand (0.6 mg, 1.7 μmol) and sodium *tert*-butoxide (22 mg, 0.23 mmol) in (trifluoromethyl)benzene

(2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **99a** as a yellow oil (30 mg, 47%). The desired product **98a** was not obtained.



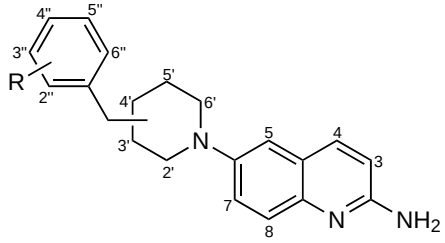
99a

*2-(*tert*-Butoxy)-6-(3-(2-pyridinylmethyl)piperidin-1-yl)quinoline (**99a**):* R_f = 0.60 (9:1 dichloromethane/methanol). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{24}H_{29}N_3O - OC(CH_3)_3$: 304.1814; found 304.1807. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.17-1.28 [1H, m, H(4'$_{ax}$)], 1.66 [9H, s, O^{t}Bu], 1.69-1.86 [3H, m, H(4'$_{eq}$) + H(5'$_{ax}$) + H(5'$_{eq}$)], 2.22-2.33 [1H, m, H(3'$_{ax}$)], 2.57 [1H, dd, $^2J_{2'ax,2'eq}$ = 11.9 Hz, $^3J_{2'ax,3'ax}$ = 10.2 Hz, H(2'$_{ax}$)], 2.72-2.87 [3H, m, H(6'$_{ax}$) + H(A)], 3.52-3.63 [2H, m, H(2'$_{eq}$) + H(6'$_{eq}$)], 6.72 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.96 [1H, d, $^4J_{5,7}$ = 2.7 Hz, H(5)], 7.11-7.18 [2H, m, H(4") + H(6")], 7.30 [1H, dd, $^3J_{7,8}$ = 9.2 Hz, $^4J_{5,7}$ = 2.7 Hz, H(7)], 7.61 [1H, td, $^3J_{4",5"} = {}^3J_{5",6"}$ = 7.7 Hz, $^4J_{3",5"}$ = 1.7 Hz, H(5")], 7.65 [1H, d, $^3J_{7,8}$ = 9.2 Hz, H(8)], 7.76 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)], 8.57 [1H, ddd, $^3J_{3",4"}$ = 4.9 Hz, $^4J_{3",5"}$ = 1.7 Hz, $^5J_{3",6"}$ = 0.8 Hz, H(3")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.18 [C(5')], 28.83 [O^{t}Bu], 30.87 [C(4')], 36.83 [C(3')], 43.08 [C(A)], 51.42 [C(6')], 56.76 [C(2')], 79.70[O^{t}Bu], 111.08 [C(5)], 115.12 [C(3)], 121.33 [C(6")], 122.99 [C(7)], 123.60 [C(4")], 125.30 [C(4a)], 128.16 [C(8)], 136.41 [C(5")], 137.22 [C(4)], 141.52 [C(8a)], 148.49 [C(6)], 149.46 [C(3")], 160.49 [C(1")], 160.57 [C(2)].

Synthesis method b. Using General Method 10, **35a** (92 mg, 0.52 mmol) and **24** (183 mg, 0.75 mmol) were reacted with $Pd(OAc)_2$ (0.4 mg, 1.8 μmol), CataCXium® A ligand (1.4 mg, 3.9 μmol) and sodium *tert*-butoxide (37 mg, 0.39 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol yielded a crude mixture containing recovered reagents.

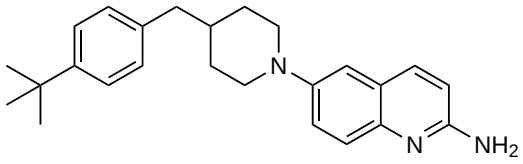
6.2.6 Synthesis of 2-aminoquinoline derivatives by Buchwald-Hartwig amination

General Method 11: Synthesis of extended 2-aminoquinolines via sealed-tube Buchwald-Hartwig amination[52]



The 2-chloroquinoline derivative (1.0 eq) was added to a glass pressure tube with $Pd(dba)_2$ (1.0 mol %) and DavePhos (1.2 mol %). 1,4-Dioxane was added followed by LiHMDS solution (1.0 M in THF, 2.2 eq) and the tube was purged with N_2 gas and sealed. The reaction mixture was heated at 100°C for 16 hr, then cooled and filtered through Celite®, washing with methanol. The solvent was removed under reduced pressure and the mixture chromatographed on silica gel with the specified eluant.

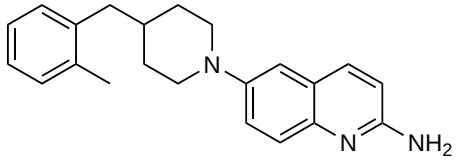
6-(4-(4-*tert*-Butylbenzyl)piperidin-1-yl)quinolin-2-amine (19a)



Using General Method 11, **82a** (50 mg, 0.13 mmol) was reacted with LiHMDS solution (1.0 M in THF, 280 μL, 0.28 mmol), $Pd(dba)_2$ (0.7 mg, 1.2 μmol) and DavePhos (0.6 mg, 1.5 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **19a** as a tan solid (42 mg, 88%). $R_f = 0.26$ (1:9 methanol/dichloromethane). MP: 184-187°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{25}H_{31}N_3$: 374.2596; found 374.2590. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 [9H, s, ^{t}Bu], 1.46 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.1$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 3.7$ Hz, $H(3'_{ax}) + H(5'_{ax})$], 1.68 [1H, ttt, $^3J_{(3'/5')ax,4'ax} = 12.1$ Hz, $^3J_{4'ax,A} = 7.2$ Hz, $^3J_{(3'/5')eq,4'ax} = 3.7$ Hz, $H(4'_{ax})$], 1.80 [2H, br d‡, $^2J_{(3'/5')ax,(3'/5')eq} = 12.1$ Hz, $H(3'_{eq}) + H(5'_{eq})$], 2.57 [2H, d, $^3J_{4'ax,A} = 7.2$ Hz, H(A)], 2.67 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = 12.1$ Hz, $^3J_{(2'/6')ax,(3'/5')eq} = 1.5$ Hz, $H(2'_{ax}) + H(6'_{ax})$], 3.67 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.1$ Hz, $H(2'_{eq}) + H(6'_{eq})$], 4.67 [2H, br s, NH_2], 6.66 [1H, d, $^3J_{3,4} = 8.7$ Hz, H(3)], 6.95 [1H, d, $^4J_{5,7} = 2.3$ Hz, H(5)], 7.07-7.15 [2H, m, H(2") + H(6")], 7.28-7.39 [3H, m, H(7) + H(3") + H(5")], 7.56 [1H, d, $^3J_{7,8} = 9.2$ Hz, H(8)], 7.75 [1H, d, $^3J_{3,4} = 8.7$ Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.57 [^{t}Bu], 32.30 [C(3') + C(5')], 34.51 [^{t}Bu], 37.86 [C(4')], 42.73

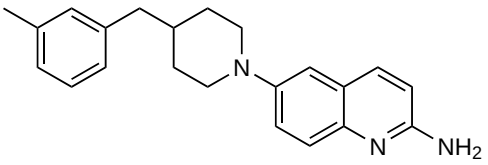
[C(A)], 50.96 [C(2') + C(6')], 111.31 [C(5)], 111.86 [C(3)], 123.72 [C(7)], 124.32 [C(4a)], 125.22 [C(3'') + C(5'')], 126.46 [C(8)], 128.94 [C(2'') + C(6'')], 137.47 [C(1'')], 137.50 [C(4)], 142.31 [C(8a)], 147.85 [C(6)], 148.81 [C(4'')], 155.41 [C(2)].

6-(4-(2-Methylbenzyl)piperidin-1-yl)quinolin-2-amine (19b)



Using General Method 11, **82b** (50 mg, 0.14 mmol) was reacted with LiHMDS solution (1.0 M in THF, 313 μL, 0.31 mmol), $Pd(dba)_2$ (0.8 mg, 1.4 μmol) and DavePhos (0.7 mg, 1.7 μmmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 3% methanol in dichloromethane gave **19b** as a yellow solid (29 mg, 61%). $R_f = 0.23$ (1:9 methanol/dichloromethane). MP: 191-193°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{25}N_3$: 332.2127; found 332.2122. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.2$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 3.8$ Hz, $H(3'_{ax}) + H(5'_{ax})$], 1.68 [1H, ttt, $^3J_{(3'/5')ax,4'ax} = 12.2$ Hz, $^3J_{4'ax,A} = 7.7$ Hz, $^3J_{(3'/5')eq,4'ax} = 3.8$ Hz, $H(4'_{ax})$], 1.80 [2H, br d‡, $^2J_{(3'/5')ax,(3'/5')eq} = 12.2$ Hz, $H(3'_{eq}) + H(5'_{eq})$], 2.33 [3H, s, CH_3], 2.61 [2H, d, $^3J_{4'ax,A} = 7.7$ Hz, H(A)], 2.66 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = 12.2$ Hz, $^3J_{(2'/6')ax,(3'/5')eq} = 2.2$ Hz, $H(2'_{ax}) + H(6'_{ax})$], 3.68 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.2$ Hz, $H(2'_{eq}) + H(6'_{eq})$], 4.66 [2H, br s, NH_2], 6.66 [1H, d, $^3J_{3,4} = 8.7$ Hz, H(3)], 6.96 [1H, d, $^4J_{5,7} = 2.7$ Hz, H(5)], 7.09-7.19 [4H, m, H(3'') + H(4'') + H(5'') + H(6'')], 7.36 [1H, dd, $^3J_{7,8} = 9.2$ Hz, $^4J_{5,7} = 2.7$ Hz, H(7)], 7.57 [1H, d, $^3J_{7,8} = 9.2$ Hz, H(8)], 7.76 [1H, d, $^3J_{3,4} = 8.7$ Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.74 [CH_3], 32.51 [C(3') + C(5')], 36.89 [C(4')], 40.41 [C(A)], 51.04 [C(2') + C(6')], 111.36 [C(5)], 111.85 [C(3)], 123.73 [C(7)], 124.37 [C(4a)], 125.78 [C(5'')], 126.17 [C(4'')], 126.60 [C(8)], 130.17 [C(6'')], 130.42 [C(3'')], 136.31 [C(2'')], 137.45 [C(4)], 138.86 [C(1'')], 142.51 [C(8a)], 147.80 [C(6)], 155.45 [C(2)].

6-(4-(3-Methylbenzyl)piperidin-1-yl)quinolin-2-amine (19c)

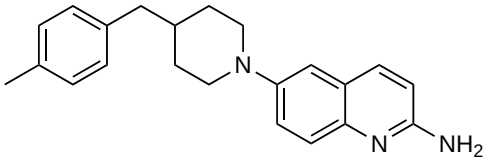


Using General Method 11, **82c** (72 mg, 0.21 mmol) was reacted with LiHMDS solution (1.0 M in THF, 450 μL, 0.45 mmol), $Pd(dba)_2$ (1.2 mg, 2.1 μmol) and DavePhos (1.0 mg, 2.5 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel

eluting with 19:1 dichloromethane/methanol gave **19c** as a yellow solid (31 mg, 46%). MP: 155-157°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{25}N_3$: 332.2127; found 332.2122. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ = 12.2 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.5 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.68 [1H, ttt, $^3J_{(3'/5')ax,4'ax}$ = 12.2 Hz, $^3J_{4'ax,A}$ = 7.1 Hz, $^3J_{(3'/5')eq,4'ax}$ = 3.5 Hz, H($4'_{ax}$)], 1.79 [2H, br d‡, $^2J_{(3'/5')ax,(3'/5')eq}$ = 12.2 Hz, H($3'_{eq}$) + H($5'_{eq}$)], 2.35 [3H, s, CH_3], 2.56 [2H, d, $^3J_{4'ax,A}$ = 7.1 Hz, H(A)], 2.67 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax}$ = 12.2 Hz, $^3J_{(2'/6')ax,(3'/5')eq}$ = 1.7 Hz, H($2'_{ax}$) + H($6'_{ax}$)], 3.68 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.2 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 4.72 [2H, br s, NH_2], 6.67 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.91-7.08 [4H, m, H(5) + H(2") + H(4") + H(6")], 7.19 [1H, t, $^3J_{4",5"} = {}^3J_{5",6"}$ = 7.5 Hz, H(5")], 7.36 [1H, dd, $^3J_{7,8}$ = 9.2 Hz, $^4J_{5,7}$ = 2.5 Hz, H(7)], 7.57 [1H, d, $^3J_{7,8}$ = 9.2 Hz, H(8)], 7.76 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.59 [CH_3], 32.33 [C(3') + C(5')], 37.97 [C(4')], 43.26 [C(A)], 50.94 [C(2') + C(6')], 111.31 [C(5)], 111.85 [C(3)], 123.76 [C(7)], 124.34 [C(4a)], 126.33 [C(6")], 126.39 [C(8)], 126.78 [C(4")], 128.25 [C(5")], 130.10 [C(2")], 137.62 [C(4)], 137.93 [C(3")], 140.57 [C(1")], *142.17 [C(8a)], 147.90 [C(6)], 155.33 [C(2)].

*The C(8a) signal was not observed in the ^{13}C NMR spectrum, and the chemical shift was instead determined using clear [^{1}H,^{13}C]-HMBC spectrum correlations with the H(4), H(5) and H(7) signals.

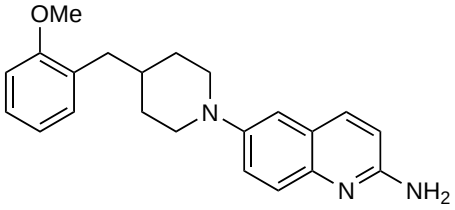
6-(4-(4-Methylbenzyl)piperidin-1-yl)quinolin-2-amine (19d)



Using General Method 11, **82d** (122 mg, 0.35 mmol) was reacted with LiHMDS solution (1.0 M in THF, 765 μL, 0.77 mmol), $Pd(dba)_2$ (2.0 mg, 3.5 μmol) and DavePhos (1.6 mg, 4.1 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **19d** as a yellow solid (43 mg, 41%). R_f = 0.36 (1:9 methanol/dichloromethane). MP: degraded 190°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{25}N_3$: 332.2127; found 332.2121. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ = 12.1 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.8 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.61 [1H, ttt, $^3J_{(3'/5')ax,4'ax}$ = 12.1 Hz, $^3J_{4'ax,A}$ = 7.3 Hz, $^3J_{(3'/5')eq,4'ax}$ = 3.8 Hz, H($4'_{ax}$)], 1.79 [2H, br d‡, $^2J_{(3'/5')ax,(3'/5')eq}$ = 12.1 Hz, H($3'_{eq}$) + H($5'_{eq}$)], 2.33 [3H, s, CH_3], 2.56 [2H, d, $^3J_{4'ax,AH}$ = 7.3 Hz, H(A)], 2.66 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax}$ = 12.1 Hz, $^3J_{(2'/6')ax,(3'/5')eq}$ = 2.1 Hz, H($2'_{ax}$) + H($6'_{ax}$)], 3.67 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.1 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 4.64 [2H, br s, NH_2], 6.66 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.95 [1H, d, $^4J_{5,7}$ = 2.7 Hz, H(5)], 7.05-7.09 [2H, m, H(3") + H(5")], 7.09-7.13 [2H, m, H(2") + H(6")], 7.35 [1H, dd, $^3J_{7,8}$ = 9.2 Hz, $^4J_{5,7}$ = 2.7 Hz, H(7)], 7.56 [1H, d, $^3J_{7,8}$ = 9.2 Hz,

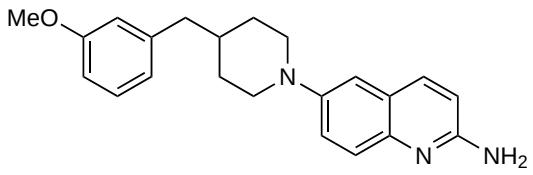
H(8)], 7.75 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.16 [CH_3], 32.30 [C(3') + C(5')], 38.04 [C(4')], 42.86 [C(A)], 50.98 [C(2') + C(6')], 111.32 [C(5)], 111.83 [C(3)], 123.71 [C(7)], 124.37 [C(4a)], 126.61 [C(8)], 129.06 [C(2'') + C(6'')], 129.17 [C(3'') + C(5'')], 135.48 [C(1'')], 137.42 [C(4)], 137.51 [C(4'')], 142.55 [C(8a)], 147.82 [C(6)], 155.44 [C(2)].

6-(4-(2-Methoxybenzyl)piperidin-1-yl)quinolin-2-amine (19e)



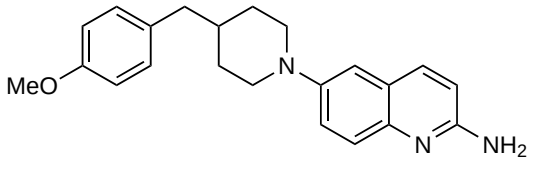
Using General Method 11, **82e** (53 mg, 0.14 mmol) was reacted with LiHMDS solution (1.0 M in THF, 318 μL, 0.32 mmol), $Pd(dba)_2$ (0.8 mg, 1.4 μmol) and DavePhos (0.7 mg, 1.8 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **19e** as a yellow solid (31 mg, 62%). R_f = 0.22 (1:9 methanol/dichloromethane). MP: 169-171°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{25}N_3O$: 348.2076; found 348.2085. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq}$ = $^3J_{(2'/6')ax,(3'/5')ax}$ = $^3J_{(3'/5')ax,4'ax}$ = 12.0 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.2 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.68-1.81 [3H, m, H($3'_{eq}$) + H($4'_{ax}$) + H($5'_{eq}$)], 2.62 [2H, d, $^3J_{4'ax,A}$ = 6.7 Hz, H(A)], 2.67 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq}$ = $^3J_{(2'/6')ax,(3'/5')ax}$ = 12.0 Hz, $^3J_{(2'/6')ax,(3'/5')eq}$ = 2.1 Hz, H($2'_{ax}$) + H($6'_{ax}$)], 3.67 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.0 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 3.83 [3H, s, OCH_3], 4.67 [2H, br s, NH_2], 6.66 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.84-6.92 [2H, m, H(3'') + H(4'')], 6.96 [1H, d, $^4J_{5,7}$ = 2.7 Hz, H(5)], 7.11 [1H, dd, $^3J_{5'',6''}$ = 7.6 Hz, $^4J_{4'',6''}$ = 1.4 Hz, H(6'')], 7.20 [1H, td, $^3J_{4'',5''}$ = $^3J_{5'',6''}$ = 7.6 Hz, $^4J_{3'',5''}$ = 1.4 Hz, H(5'')], 7.36 [1H, dd, $^3J_{7,8}$ = 9.2 Hz, $^4J_{5,7}$ = 2.7 Hz, H(7)], 7.56 [1H, d, $^3J_{7,8}$ = 9.2 Hz, H(8)], 7.76 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.41 [C(3') + C(5')], 36.32 [C(4')], 37.32 [C(A)], 50.98 [C(2') + C(6')], 55.41 [OCH_3], 110.48 [C(3'')], 111.26 [C(5)], 111.82 [C(3)], 120.29 [C(5'')], 123.73 [C(7)], 124.38 [C(4a)], 126.51 [C(8)], 127.29 [C(1'')], 129.08 [C(4'')], 131.09 [C(6'')], 137.47 [C(4)], 142.40 [C(8a)], 147.92 [C(6)], 155.40 [C(2)], 157.81 [C(2'')].

6-(4-(3-Methoxybenzyl)piperidin-1-yl)quinolin-2-amine (19f)



Using General Method 11, **82f** (82 mg, 0.22 mmol) was treated with LiHMDS solution (1.0 M in THF, 490 μL, 0.49 mmol), $Pd(dba)_2$ (1.3 mg, 2.3 μmol) and DavePhos (1.1 mg, 2.8 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **19f** as a yellow solid (72 mg, 93%). R_f = 0.10 (1:9 methanol/dichloromethane). MP: degraded 160°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{25}N_3O$: 348.2078; found 348.2069. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ = 12.2 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.9 Hz, $H(3'_{ax}) + H(5'_{ax})$], 1.70 [1H, ttt, $^3J_{(3'/5')ax,4'ax}$ = 12.2 Hz, $^3J_{4'ax,A}$ = 7.6 Hz, $^3J_{(3'/5')eq,4'ax}$ = 3.9 Hz, $H(4'_{ax})$], 1.80 [2H, br d‡, $^2J_{(3'/5')ax,(3'/5')eq}$ = 12.2 Hz, $H(3'_{eq}) + H(5'_{eq})$], 2.58 [2H, d, $^3J_{4'ax,A}$ = 7.6 Hz, H(A)], 2.68 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax}$ = 12.2 Hz, $^3J_{(2'/6')ax,(3'/5')eq}$ = 1.8 Hz, $H(2'_{ax}) + H(6'_{ax})$], 3.68 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.2 Hz, $H(2'_{eq}) + H(6'_{eq})$], 3.81 [3H, s, OCH_3], 4.78 [2H, br s, NH_2], 6.68 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.71-6.81 [3H, m, H(2") + H(4") + H(6")], 6.96 [1H, d, $^4J_{5,7}$ = 2.6 Hz, H(5)], 7.22 [1H, t, $^3J_{4",5"} = {}^3J_{5",6"}$ = 7.8 Hz, H(5")], 7.36 [1H, dd, $^3J_{7,8}$ = 9.2 Hz, $^4J_{5,7}$ = 2.6 Hz, H(7)], 7.57 [1H, d, $^3J_{7,8}$ = 9.2 Hz, H(8)], 7.77 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.28 [C(3') + C(5')], 37.87 [C(4')], 43.33 [C(A)], 50.89 [C(2') + C(6')], 55.30 [OCH_3], 111.13 [C(4")], 111.34 [C(5)], 111.96 [C(3)], 115.18 [C(2")], 121.76 [C(6")], 123.80 [C(7)], 124.21 [C(4a)], 126.02 [C(8)], 129.31 [C(5")], 137.83 [C(4)], 141.56 [C(1")], 142.25 [C(8a)], 147.92 [C(6)], 155.28 [C(2)], 159.70 [C(3")].

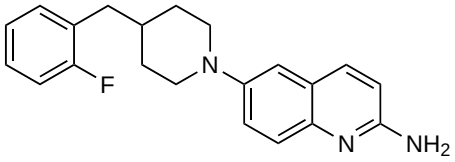
6-(4-(4-Methoxybenzyl)piperidin-1-yl)quinolin-2-amine (19g)



Using General Method 11, **82g** (30 mg, 0.08 mmol) was reacted with LiHMDS solution (1.0 M in THF, 180 μL, 0.18 mmol), $Pd(dba)_2$ (0.5 mg, 0.8 μmol) and DavePhos (0.4 mg, 1.0 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **19g** as a tan solid (16 mg, 56%). MP: 172-174°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{25}N_3O$: 348.2076; found 348.2069. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$

= 12.2 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.6 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.70 [1H, ttt, $^{3}J_{(3'/5')ax,4'ax}$ = 12.2 Hz, $^{3}J_{4'ax,A}$ = 7.1 Hz, $^{3}J_{(3'/5')eq,4'ax}$ = 3.6 Hz, H($4'_{ax}$)], 1.78 [2H, br d‡, $^{2}J_{(3'/5')ax,(3'/5')eq}$ = 12.2 Hz, H($3'_{eq}$) + H($5'_{eq}$)], 2.54 [2H, d, $^{3}J_{4'ax,A}$ = 7.1 Hz, H(A)], 2.67 [2H, td, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = 12.2 Hz, $^{3}J_{(2'/6')ax,(3'/5')eq}$ = 2.1 Hz, H($2'_{ax}$) + H($6'_{ax}$)], 3.67 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.2 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 3.80 [3H, s, OCH_3], 4.81 [2H, br s, NH_2], 6.66 [1H, d, $^{3}J_{3,4}$ = 8.7 Hz, H(3)], 6.81-6.88 [2H, m, H(3") + H(5")], 6.95 [1H, d, $^{4}J_{5,7}$ = 2.7 Hz, H(5)], 7.05-7.12 [2H, m, H(2") + H(6")], 7.35 [1H, dd, $^{3}J_{7,8}$ = 9.2 Hz, $^{4}J_{5,7}$ = 2.7 Hz, H(7)], 7.57 [1H, d, $^{3}J_{7,8}$ = 9.2 Hz, H(8)], 7.76 [1H, d, $^{3}J_{3,4}$ = 8.7 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.25 [C(3') + C(5')], 38.13 [C(4')], 42.38 [C(A)], 50.95 [C(2') + C(6')], 55.42 [OCH_3], 111.33 [C(5)], 111.91 [C(3)], 113.81 [C(3") + C(5")], 123.75 [C(7)], 124.29 [C(4a)], 126.32 [C(8)], 130.15 [C(2") + C(6")], 132.68 [C(1")], 137.60 [C(4)], 142.12 [C(8a)], 147.87 [C(6)], 155.41 [C(2)], 158.02 [C(4")].

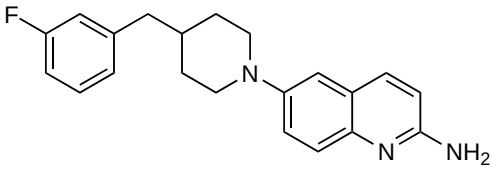
6-(4-(2-Fluorobenzyl)piperidin-1-yl)quinolin-2-amine (19h)



Using General Method 11, **82h** (17 mg, 0.05 mmol) was reacted with LiHMDS solution (1.0 M in THF, 105 μL, 0.10 mmol), $Pd(dba)_2$ (0.3 mg, 0.5 μmol) and DavePhos (0.2 mg, 0.5 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **19h** as a yellow solid (14 mg, 87%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{22}FN_3$: 336.1876; found 336.1871. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 [2H, qd, $^{2}J_{(3'/5')ax,(3'/5')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = $^{3}J_{(3'/5')ax,4'ax}$ = 12.1 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.7 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.68-1.84 [3H, m, H($4'_{ax}$) + H($3'_{eq}$) + H($5'_{eq}$)], 2.61-2.73 [4H, m, H(A) + H($2'_{ax}$) + H($6'_{ax}$)], 3.68 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.1 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 4.96 [2H, br s, NH_2], 6.69 [1H, d, $^{3}J_{3,4}$ = 8.8 Hz, H(3)], 6.96 [1H, d, $^{4}J_{5,7}$ = 2.7 Hz, H(5)], 7.00-7.10 [2H, m, H(3") + H(5")], 7.14-7.23 [2H, m, H(4") + H(6")], 7.36 [1H, dd, $^{3}J_{7,8}$ = 9.2 Hz, $^{4}J_{5,7}$ = 2.7 Hz, H(7)], 7.58 [1H, d, $^{3}J_{7,8}$ = 9.2 Hz, H(8)], 7.77 [1H, d, $^{3}J_{3,4}$ = 8.8 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.18 [C(3') + C(5')], 36.17 [C(A)], 36.90 [C(4')], 50.81 [C(2') + C(6')], 111.35 [C(5)], 111.97 [C(3)], 115.39 [d, $^{2}J_{C,F}$ = 22.5 Hz, C(3")], 123.83 [br, C(7)], 123.92 [d, $^{4}J_{C,F}$ = 3.6 Hz, C(5")], 124.20 [br, C(4a)], 125.90 [br, C(8)], 127.42 [d, $^{2}J_{C,F}$ = 16.1 Hz, C(1")], 127.86 [d, $^{3}J_{C,F}$ = 8.0 Hz, C(4")], 131.71 [d, $^{3}J_{C,F}$ = 5.1 Hz, C(6")], 137.95 [C(4)], *141.34 [C(8a)], 147.95 [C(6)], 155.22 [C(2)], 161.45 [d, $^{1}J_{C,F}$ = 244.5 Hz, C(2")].

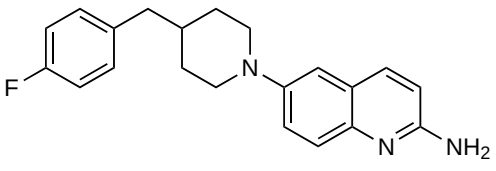
*The C(8a) signal was not observed in the ^{13}C NMR spectrum, and the chemical shift was instead determined using clear [^{1}H,^{13}C]-HMBC spectrum correlations with the H(4), H(5) and H(7) signals.

6-(4-(3-Fluorobenzyl)piperidin-1-yl)quinolin-2-amine (19i)



Using General Method 11, **82i** (159 mg, 0.45 mmol) was reacted with LiHMDS solution (1.0 M in THF, 980 μL, 0.98 mmol), $Pd(dba)_2$ (2.6 mg, 4.5 μmol) and DavePhos (2.1 mg, 5.3 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **19i** as a yellow solid (67 mg, 45%). $R_f = 0.18$ (1:9 methanol/dichloromethane). MP: 158-161°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{22}FN_3$: 336.1876; found 336.1869. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.1$ Hz, $^3J_{(2'/6')eq,(3'/5)ax} = 3.7$ Hz, $H(3'_{ax}) + H(5'_{ax})$], 1.64-1.84 [3H, m, $H(4'_{ax}) + H(3'_{eq}) + H(5'_{eq})$], 2.60 [2H, d, $^3J_{4'ax,A} = 7.1$ Hz, H(A)], 2.68 [2H, br t‡, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = 12.1$ Hz, $H(2'_{ax}) + H(6'_{ax})$], 3.68 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.1$ Hz, $H(2'_{eq}) + H(6'_{eq})$], 5.00 [2H, br s, NH_2], 6.70 [1H, d, $^3J_{3,4} = 8.8$ Hz, H(3)], 6.85-7.00 [4H, m, H(5) + H(2") + H(4") + H(6")], 7.25 [1H, q, $^3J_{4",5"} = {}^3J_{5",6"} = {}^4J_{H,F} = 7.6$ Hz, H(5")], 7.36 [1H, dd, $^3J_{7,8} = 9.1$ Hz, $^4J_{5,7} = 2.0$ Hz, H(7)], 7.58 [1H, d, $^3J_{7,8} = 9.1$ Hz, H(8)], 7.78 [1H, d, $^3J_{3,4} = 8.8$ Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.20 [C(3') + C(5')], 37.81 [C(4')], 43.01 [C(A)], 50.89 [C(2') + C(6')], 111.39 [C(5)], 111.90 [C(3)], 112.95 [d, $^2J_{C,F} = 21.0$ Hz, C(4")], 116.02 [d, $^2J_{C,F} = 20.5$ Hz, C(2")], 123.78 [C(7)], 124.29 [C(4a)], 124.95 [d, $^4J_{C,F} = 2.9$ Hz, C(6")], 126.36 [C(8)], 129.76 [d, $^3J_{C,F} = 8.6$ Hz, C(5")], 137.66 [C(4)], 143.17 [d, $^3J_{C,F} = 6.9$ Hz, C(1")], 147.80 [C(6)], 155.37 [C(2)], 163.01 [d, $^1J_{C,F} = 245.5$ Hz, C(3")].

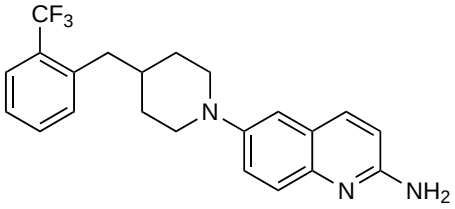
6-(4-(4-Fluorobenzyl)piperidin-1-yl)quinolin-2-amine (19j)



Using General Method 11, **82j** (89 mg, 0.25 mmol) was reacted with LiHMDS solution (1.0 M in THF, 554 μL, 0.55 mmol), $Pd(dba)_2$ (1.4 mg, 2.4 μmol) and DavePhos (1.2 mg, 3.0 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **19j** as a yellow solid (24 mg, 29%). $R_f = 0.26$ (9:1 dichloromethane/methanol). MP: 224-227°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{22}FN_3$: 336.1876; found 336.1868. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 11.9$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 3.8$ Hz, $H(3'_{ax}) + H(5'_{ax})$],

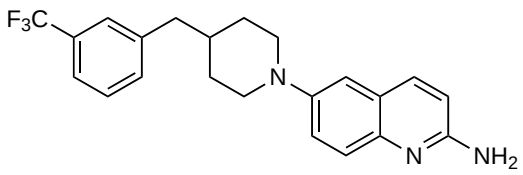
1.65 [1H, ttt, $^{3}J_{(3'/5')ax,4'ax}$ = 11.9 Hz, $^{3}J_{4'ax,A}$ = 7.7 Hz, $^{3}J_{(3'/5')eq,4'ax}$ = 3.8 Hz, H($4'_{ax}$)], 1.77 [2H, br d‡, $^{2}J_{(3'/5')ax,(3'/5')eq}$ = 11.9 Hz, H($3'_{eq}$) + H($5'_{eq}$)], 2.57 [2H, d, $^{3}J_{4'ax,A}$ = 7.7 Hz, H(A)], 2.67 [2H, td, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = 11.9 Hz, $^{3}J_{(2'/6')ax,(3'/5')eq}$ = 2.2 Hz, H($2'_{ax}$) + H($6'_{ax}$)], 3.68 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 11.9 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 4.65 [2H, br s, NH_2], 6.66 [1H, d, $^{3}J_{3,4}$ = 8.7 Hz, H(3)], 6.94-7.01 [3H, m, H(5) + H(3") + H(5")], 7.09-7.15 [2H, m, H(2") + H(6")], 7.35 [1H, dd, $^{3}J_{7,8}$ = 9.2 Hz, $^{4}J_{5,7}$ = 2.7 Hz, H(7)], 7.56 [1H, d, $^{3}J_{7,8}$ = 9.2 Hz, H(8)], 7.75 [1H, d, $^{3}J_{3,4}$ = 8.7 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.18 [C(3') + C(5')], 38.04 [C(4')], 42.43 [C(A)], 50.94 [C(2') + C(6')], 111.37 [C(5)], 111.86 [C(3)], 115.12 [d, $^{2}J_{C,F}$ = 21.0 Hz, C(3") + C(5")], 123.71 [C(7)], 124.35 [C(4a)], 126.62 [C(8)], 130.55 [d, $^{3}J_{C,F}$ = 7.6 Hz, C(2") + C(6")], 136.16 [d, $^{4}J_{C,F}$ = 3.3 Hz, C(1")], 137.44 [C(4)], 142.54 [C(8a)], 147.74 [C(6)], 155.46 [C(2)], 161.49 [d, $^{1}J_{C,F}$ = 243.7 Hz, C(4")].

6-(4-(2-(Triflurorομethyl)benzyl)piperidin-1-yl)quinolin-2-amine (19n)



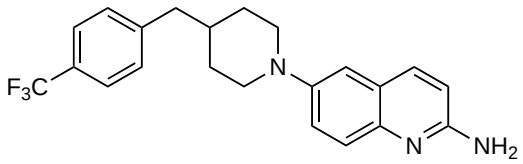
Using General Method 11, **82n** (77 mg, 0.19 mmol) was reacted with LiHMDS solution (1.0 M in THF, 440 μL, 0.44 mmol), $Pd(dba)_2$ (1.1 mg, 1.9 μmol) and DavePhos (0.9 mg, 2.3 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **19n** as a yellow solid (47 mg, 63%). R_f = 0.20 (1:9 methanol/dichloromethane). MP: 160-163°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{22}F_3N_3$: 386.1844; found 386.1848. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53 [2H, qd, $^{2}J_{(3'/5')ax,(3'/5')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = $^{3}J_{(3'/5')ax,4'ax}$ = 12.1 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 2.9 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.71-1.84 [3H, m, H($4'_{ax}$) + H($3'_{eq}$) + H($5'_{eq}$)], 2.67 [2H, br t‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = 12.1 Hz, H($2'_{ax}$) + H($6'_{ax}$)], 2.79 [2H, d, $^{3}J_{4'ax,A}$ = 6.4 Hz, H(A)], 3.69 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.1 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 4.66 [2H, br s, NH_2], 6.66 [1H, d, $^{3}J_{3,4}$ = 8.7 Hz, H(3)], 6.98 [1H, d, $^{4}J_{5,7}$ = 2.5 Hz, H(5)], 7.28-7.39 [3H, m, H(7) + H(4") + H(6")], 7.48 [1H, t, $^{3}J_{4",5"}$ = $^{3}J_{5",6"}$ = 7.7 Hz, H(5")], 7.57 [1H, d, $^{3}J_{7,8}$ = 9.2 Hz, H(8)], 7.65 [1H, d, $^{3}J_{3",4"}$ = 7.7 Hz, H(3")], 7.75 [1H, d, $^{3}J_{3,4}$ = 8.7 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.38 [C(3') + C(5')], 37.58 [C(4')], 39.56 [C(A)], 51.00 [C(2') + C(6')], 111.41 [C(5)], 111.86 [C(3)], 123.69 [C(7)], 124.35 [C(4a)], 124.78 [q, $^{1}J_{C,F}$ = 273.9 Hz, CF_3], 126.23 [C(8)], 126.31 [q, $^{3}J_{C,F}$ = 5.7 Hz, C(3")], 126.63 [C(5")], 129.02 [q, $^{2}J_{C,F}$ = 29.6 Hz, C(2")], 131.50 [br‡, C(6")], 131.90 [C(4")], 137.42 [C(4)], 139.26 [q, $^{3}J_{C,F}$ = 1.6 Hz, C(1")], 142.60 [C(8a)], 147.71 [C(6)], 155.50 [C(2)].

6-(4-(3-(Triflurorometh yl)benzyl)piperidin-1-yl)quinolin-2-amine (19o)



Using General Method 11, **82o** (38 mg, 0.09 mmol) was reacted with LiHMDS solution (1.0 M in THF, 206 μL, 0.21 mmol), $Pd(dba)_2$ (0.5 mg, 1.4 μmol) and DavePhos (0.4 mg, 0.7 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **19n** as a yellow solid (23 mg, 64%). MP: 116-119°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{22}F_3N_3$: 386.1844; found 386.1836. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ = 12.0 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.4 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.64-1.84 [3H, m, H(4'$_{ax}$) + H(3'$_{eq}$) + H(5'$_{eq}$)], 2.61-2.73 [4H, m, H(A) + H(2'$_{ax}$) + H(6'$_{ax}$)], 3.68 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.0 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 4.71 [2H, br s, NH_2], 6.67 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.96 [1H, d, $^4J_{5,7}$ = 2.6 Hz, H(5)], 7.32-7.38 [2H, m, H(7) + H(6")], 7.38-7.45 [2H, m, H(2") + H(5")], 7.47 [1H, br d‡, $^3J_{4",5"}$ = 7.7 Hz, H(4")], 7.57 [1H, d, $^3J_{7,8}$ = 9.2 Hz, H(8)], 7.76 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.15 [C(3') + C(5')], 37.85 [C(4')], 43.06 [C(A)], 50.87 [C(2') + C(6')], 111.42 [C(5)], 111.90 [C(3)], 123.01 [q, $^3J_{C,F}$ = 3.8 Hz, C(4")], 123.70 [C(7)], 124.32 [C(4a)], 124.40 [q, $^1J_{C,F}$ = 272.3 Hz, CF_3], 125.84 [q, $^3J_{C,F}$ = 3.8 Hz, C(2")], 126.56 [C(8)], 128.79 [C(5")], 130.75 [q, $^2J_{C,F}$ = 31.9 Hz, C(3")], 132.68 [q, $^5J_{C,F}$ = 1.0 Hz, C(6")], 137.49 [C(4)], 141.45 [C(1")], 142.44 [C(8a)], 147.68 [C(6)], 155.48 [C(2)].

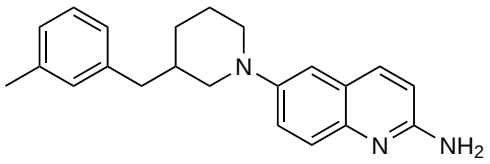
6-(4-(4-(Triflurorometh yl)benzyl)piperidin-1-yl)quinolin-2-amine (19p)



Using General Method 11, **82p** (125 mg, 0.31 mmol) was reacted with LiHMDS solution (1.0 M in THF, 680 μL, 0.68 mmol), $Pd(dba)_2$ (1.8 mg, 3.1 μmol) and DavePhos (1.5 mg, 3.8 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 4% methanol in dichloromethane gave **19p** as a tan solid (39 mg, 33%). R_f = 0.38 (1:9 methanol/dichloromethane). MP: 140-142°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{22}F_3N_3$: 386.1844; found 386.1838. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ = 12.0 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.2 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.65-1.82 [3H, m, H(4'$_{ax}$) + H(3'$_{eq}$) + H(5'$_{eq}$)], 2.61-2.72 [4H, m, H(A) +

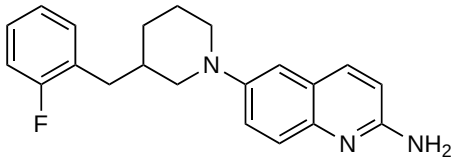
H(2'$_{ax}$) + H(6'$_{ax}$)], 3.68 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.0 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 4.84 [2H, br s, NH_2], 6.67 [1H, d, $^{3}J_{3,4}$ = 8.8 Hz, H(3)], 6.95 [1H, d, $^{4}J_{5,7}$ = 2.6 Hz, H(5)], 7.26-7.32 [2H, m, H(2") + H(6")], 7.35 [1H, dd, $^{3}J_{7,8}$ = 9.2 Hz, $^{4}J_{5,7}$ = 2.6 Hz, H(7)], 7.52-7.61 [3H, m, H(8) + H(3") + H(5")], 7.76 [1H, d, $^{3}J_{3,4}$ = 8.8 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.20 [C(3') + C(5')], 37.82 [C(4')], 43.08 [C(A)], 50.87 [C(2') + C(6')], 111.43 [C(5)], 111.96 [C(3)], 123.74 [C(7)], 124.26 [C(4a)], 124.50 [q, $^{1}J_{C,F}$ = 271.8 Hz, CF_3], 125.33 [q, $^{3}J_{C,F}$ = 3.8 Hz, C(3") + C(5")], 126.33 [C(8)], 128.49 [q, $^{2}J_{C,F}$ = 31.9 Hz, C(4")], 129.55 [C(2") + C(6")], 137.62 [C(4)], 142.13 [br, C(8a)], 144.70 [br‡, C(1")], 147.72 [C(6)], 155.45 [C(2)].

6-(3-(3-methylbenzyl)piperidin-1-yl)quinolin-2-amine (20c)



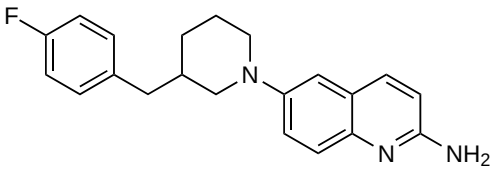
Using General Method 11, **83c** (70 mg, 0.20 mmol) was reacted with LiHMDS solution (1.0 M in THF, 439 μL, 0.44 mmol), $Pd(dba)_2$ (1.1 mg, 1.9 μmol) and DavePhos (0.9 mg, 2.3 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 9:1 dichloromethane/methanol with 0.001% triethylamine gave **20c** as a yellow oil (52 mg, 79%). R_f = 0.37 (9:1 dichloromethane/methanol). MP: 102-105°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{25}N_3$: 332.2127; found 332.2124. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 [1H, qd, $^{2}J_{4'ax,4'eq} = {}^{3}J_{3'ax,4'ax} = {}^{3}J_{4'ax,5'ax}$ = 11.5 Hz, $^{3}J_{4'ax,5'eq}$ = 4.3 Hz, H(4'$_{ax}$)], 1.69 [1H, qt, $^{2}J_{5'ax,5'eq} = {}^{3}J_{4'ax,5'ax} = {}^{3}J_{5'ax,6'ax}$ = 11.5 Hz, $^{3}J_{4'eq,5'ax} = {}^{3}J_{5'ax,6'eq}$ = 4.3 Hz, H(5'$_{ax}$)], 1.76-1.87 [2H, m, H(4'$_{eq}$) + H(5'$_{eq}$)], 2.03 [1H, ttt, $^{3}J_{2'ax,3'ax} = {}^{3}J_{3'ax,4'ax}$ = 11.5 Hz, $^{3}J_{3'ax,A} = {}^{3}J_{3'ax,A'}$ = 7.6 Hz, $^{3}J_{2'eq,3'ax} = {}^{3}J_{3'ax,4'eq}$ = 3.8 Hz, H(3'$_{ax}$)], 2.34 [1H, s, CH_3], 2.49 [1H, t, $^{2}J_{2'ax,2'eq} = {}^{3}J_{2'ax,3'ax}$ = 11.5 Hz, H(2'$_{ax}$)], 2.55 [1H, dd, $^{2}J_{A,A'}$ = 13.5 Hz, $^{3}J_{3'ax,A}$ = 7.6 Hz, H(A)], 2.61 [1H, dd, $^{2}J_{A,A'}$ = 13.5 Hz, $^{3}J_{3'ax,A'}$ = 7.6 Hz, H(A')], 2.74 [1H, td, $^{2}J_{6'ax,6'eq} = {}^{3}J_{5'ax,6'ax}$ = 11.5 Hz, $^{3}J_{5'eq,6'ax}$ = 2.4 Hz, H(6'$_{ax}$)], 3.51-3.61 [2H, m, H(2'$_{eq}$) + H(6'$_{eq}$)], 4.65 [2H, br s, NH_2], 6.65 [1H, d, $^{3}J_{3,4}$ = 8.7 Hz, H(3)], 6.91 [1H, d, $^{4}J_{5,7}$ = 2.3 Hz, H(5)], 6.97-7.06 [3H, m, H(2") + H(4") + H(6")], 7.19 [1H, t, $^{3}J_{4",5"} = {}^{3}J_{5",6"}$ = 7.5 Hz, H(5")], 7.30 [1H, dd, $^{3}J_{7,8}$ = 9.1 Hz, $^{4}J_{5,7}$ = 2.3 Hz, H(7)], 7.54 [1H, d, $^{3}J_{7,8}$ = 9.1 Hz, H(8)], 7.73 [1H, d, $^{3}J_{3,4}$ = 8.7 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.43 [CH_3], 25.15 [C(5')], 30.69 [C(4')], 37.76 [C(3')], 40.68 [C(A)], 51.23 [C(6')], 56.75 [C(2')], 111.18 [C(5)], 111.68 [C(3)], 123.57 [C(7)], 124.23 [C(4a)], 126.07 [C(6")], 126.44 [C(8)], 126.71 [C(4")], 128.18 [C(5")], 129.85 [C(2")], 137.26 [C(4)], 137.83 [C(1")], 140.15 [C(3")], 142.33 [C(8a)], 147.74 [C(6)], 155.29 [C(2)].

6-(3-(2-Fluorobenzyl)piperidin-1-yl)quinolin-2-amine (20h)



Using General Method 11, **83h** (14 mg, 0.04 mmol) was reacted with LiHMDS solution (1.0 M in THF, 87 μL, 0.09 mmol), $Pd(dba)_2$ (0.2 mg, 0.4 μmol) and DavePhos (0.2 mg, 0.5 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 3% methanol in dichloromethane with 0.001% triethylamine gave **20h** as a yellow solid (10 mg, 78%). R_f = 0.40 (9:1 dichloromethane/methanol). MP: 166-168°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{22}FN_3$: 336.1876; found 336.1874. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12-1.23 [1H, m, H(4'$_{ax}$)], 1.63-1.76 [1H, m, H(5'$_{ax}$)], 1.77-1.90 [2H, m, H(4'$_{eq}$) + H(5'$_{eq}$)], 2.06 [1H, ttt, $^3J_{2'ax,3'ax} = {}^3J_{3'ax,4'ax}$ = 10.6 Hz, $^3J_{3'ax,A} = {}^3J_{3'ax,A'}$ = 7.0 Hz, $^3J_{2'eq,3'ax} = {}^3J_{3'ax,4'eq}$ = 3.7 Hz, H(3'$_{ax}$)], 2.53 [1H, dd, $^2J_{2'ax,2'eq}$ = 11.4 Hz, $^3J_{2'ax,3'ax}$ = 10.6 Hz, H(2'$_{ax}$)], 2.59-2.80 [3H, m, H(6'$_{ax}$) + H(A) + H(A')], 3.50-3.63 [2H, m, H(2'$_{eq}$) + H(6'$_{eq}$)], 4.87 [2H, br s, NH_2], 6.67 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.92 [1H, d, $^4J_{5,7}$ = 2.6 Hz, H(5)], 6.99-7.11 [2H, m, H(3'') + H(5'')], 7.16-7.24 [2H, m, H(4'') + H(6'')], 7.30 [1H, dd, $^3J_{7,8}$ = 9.1 Hz, $^4J_{5,7}$ = 2.6 Hz, H(7)], 7.55 [1H, d, $^3J_{7,8}$ = 9.1 Hz, H(8)], 7.75 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.29 [C(5')], 30.66 [C(4')], 33.76 [d, $^3J_{C,F}$ = 1.4 Hz, C(A)], 37.08 [d, $^4J_{C,F}$ = 1.3 Hz, C(3')], 51.41 [C(6')], 56.75 [C(2')], 111.42 [C(5)], 111.87 [C(3)], 115.43 [d, $^2J_{C,F}$ = 22.4 Hz, C(3'')], 123.83 [C(7)], 124.01 [d, $^4J_{C,F}$ = 3.8 Hz, C(5'')], 124.30 [C(4a)], 126.36 [br, C(8)], 127.24 [d, $^2J_{C,F}$ = 15.7 Hz, C(1'')], 127.92 [d, $^3J_{C,F}$ = 8.1 Hz, C(4'')], 131.51 [d, $^3J_{C,F}$ = 5.3 Hz, C(6'')], 137.60 [C(4)], 142.15 [C(8a)], 147.95 [C(6)], 155.39 [C(2)], 161.43 [d, $^1J_{C,F}$ = 244.6 Hz, C(2'')].

6-(3-(4-Fluorobenzyl)piperidin-1-yl)quinolin-2-amine (20j)

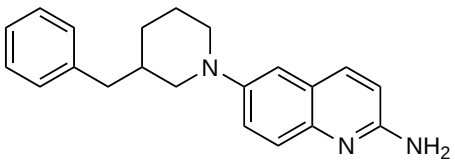


Using General Method 11, **83j** (98 mg, 0.28 mmol) was reacted with LiHMDS solution (1.0 M in THF, 610 μL, 0.61 mmol), $Pd(dba)_2$ (1.6 mg, 2.8 μmol) and DavePhos (1.3 mg, 3.3 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol with 0.001% triethylamine gave **20j** as a yellow oil (48 mg, 52%). MP: 146-148°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{22}FN_3$: 336.1876; found 336.1872. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06-1.20 [1H, m, H(4'$_{ax}$)], 1.69 [1H, qt, $^2J_{5'ax,5'eq}$

$= {}^3J_{4'ax,5'ax} = {}^3J_{5'ax,6'ax} = 12.0$ Hz, ${}^3J_{4'eq,5'ax} = {}^3J_{5'ax,6'eq} = 4.2$ Hz, H($5'_{ax}$)], 1.77-1.86 [2H, m, H($4'_{eq}$) + H($5'_{eq}$)], 1.99 [1H, ttt, ${}^3J_{2'ax,3'ax} = {}^3J_{3'ax,4'ax} = 10.6$ Hz, ${}^3J_{3'ax,A} = {}^3J_{3'ax,A'} = 7.3$ Hz, ${}^3J_{2'eq,3'ax} = {}^3J_{3'ax,4'eq} = 3.4$ Hz, H($3'_{ax}$)], 2.48 [1H, dd, ${}^2J_{2'ax,2'eq} = 11.3$ Hz, ${}^3J_{2'ax,3'ax} = 10.6$ Hz, H($2'_{ax}$)], 2.56 and 2.66 [2H, *ABX*, *A*:dd, *B*:dd, ${}^2J_{A,A'}(J_{AB}) = 13.7$ Hz, ${}^3J_{A,3'ax}(J_{AX}) = 7.3$ Hz, ${}^3J_{A',3'ax}(J_{BX}) = 7.3$ Hz, H(A) + H(A')], 2.74 [1H, td, ${}^2J_{6'ax,6'eq} = {}^3J_{5'ax,6'ax} = 12.0$ Hz, ${}^3J_{5'eq,6'ax} = 2.5$ Hz, H($6'_{ax}$)], 3.48-3.62 [2H, m, H($2'_{eq}$) + H($6'_{eq}$)], 4.78 [2H, br s, NH_2], 6.67 [1H, d, ${}^3J_{3,4} = 8.8$ Hz, H(3)], 6.91 [1H, d, ${}^4J_{5,7} = 2.6$ Hz, H(5)], 6.95-7.03 [2H, m, H(3") + H(5")], 7.10-7.18 [2H, m, H(2") + H(6")], 7.29 [1H, dd, ${}^3J_{7,8} = 9.1$ Hz, ${}^4J_{5,7} = 2.6$ Hz, H(7)], 7.55 [1H, d, ${}^3J_{7,8} = 9.1$ Hz, H(8)], 7.75 [1H, d, ${}^3J_{3,4} = 8.8$ Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.25 [C(5')], 30.68 [C(4')], 38.07 [C(3')], 40.05 [C(A)], 51.33 [C(6')], 56.70 [C(2')], 111.39 [C(5)], 111.94 [C(3)], 115.24 [d, ${}^2J_{C,F} = 21.0$ Hz, C(3") + C(5")], 123.83 [C(7)], 124.22 [C(4a)], 126.04 [br, C(8)], 130.47 [d, ${}^3J_{C,F} = 8.1$ Hz, C(2") + C(6")], 135.92 [d, ${}^4J_{C,F} = 3.2$ Hz, C(1")], 137.86 [C(4)], *142.17 [C(8a)], 148.00 [C(6)], 155.25 [C(2)], 161.54 [d, ${}^1J_{C,F} = 243.6$ Hz, C(4")].

*The C(8a) signal was not observed in the ^{13}C NMR spectrum, and the chemical shift was instead determined using clear [^{1}H,^{13}C]-HMBC spectrum correlations with the H(4), H(5) and H(7) signals.

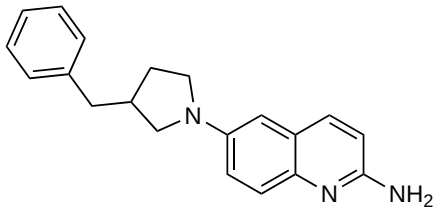
6-(3-Benzylpiperidin-1-yl)quinolin-2-amine (20x)



Using General Method 11, **83x** (94 mg, 0.28 mmol) was reacted with LiHMDS solution (1.0 M in THF, 614 μL, 0.61 mmol), $Pd(dba)_2$ (1.6 mg, 2.8 μmol) and DavePhos (1.3 mg, 3.3 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol with 0.001% triethylamine gave **20x** as a yellow oil (35 mg, 40%). $R_f = 0.07$ (19:1 dichloromethane/methanol). MP: degraded 145°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{23}N_3$: 318.1970; found 318.1979. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08-1.19 [1H, m, H($4'_{ax}$)], 1.69 [1H, qt, ${}^2J_{5'ax,5'eq} = {}^3J_{4'ax,5'ax} = {}^3J_{5'ax,6'ax} = 12.0$ Hz, ${}^3J_{4'eq,5'ax} = {}^3J_{5'ax,6'eq} = 4.3$ Hz, H($5'_{ax}$)], 1.76-1.87 [2H, m, H($4'_{eq}$) + H($5'_{eq}$)], 2.04 [1H, ttt, ${}^3J_{2'ax,3'ax} = {}^3J_{3'ax,4'ax} = 10.4$ Hz, ${}^3J_{3'ax,A} = {}^3J_{3'ax,A'} = 7.2$ Hz, ${}^3J_{2'eq,3'ax} = {}^3J_{3'ax,4'eq} = 3.3$ Hz, H($3'_{ax}$)], 2.48 [1H, dd, ${}^2J_{2'ax,2'eq} = 11.5$ Hz, ${}^3J_{2'ax,3'ax} = 10.4$ Hz, H($2'_{ax}$)], 2.58 [1H, dd, ${}^2J_{A,A'} = 13.5$ Hz, ${}^3J_{3'ax,A} = 7.2$ Hz, H(A)], 2.61 [1H, dd, ${}^2J_{A,A'} = 13.5$ Hz, ${}^3J_{3'ax,A'} = 7.2$ Hz, H(A')], 2.73 [1H, td, ${}^2J_{6'ax,6'eq} = {}^3J_{5'ax,6'ax} = 12.0$ Hz, ${}^3J_{5'eq,6'ax} = 2.3$ Hz, H($6'_{ax}$)], 3.51-3.62 [2H, m, H($2'_{eq}$) + H($6'_{eq}$)], 4.66 [2H, br s, NH_2], 6.65 [1H, d, ${}^3J_{3,4} = 8.7$ Hz, H(3)], 6.90 [1H, d, ${}^4J_{5,7} = 2.6$ Hz, H(5)], 7.16-7.24 [3H, m, H(2") + H(4") + H(6")], 7.27-7.34 [3H, m, H(7) + H(3") + H(5")], 7.54 [1H, d, ${}^3J_{7,8} = 9.1$ Hz, H(8)], 7.72

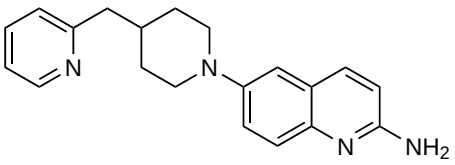
[1H, d, $^3J_{3,4}$ = 8.7 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.30 [C(5')], 30.76 [C(4')], 37.94 [C(3')], 40.91 [C(A)], 51.38 [C(6')], 56.86 [C(2')], 111.33 [C(5)], 111.81 [C(3)], 123.69 [C(7)], 124.34 [C(4a)], 126.10 [C(8)], 126.62 [C(4")], 128.43 [C(3") + C(5")], 129.17 [C(2") + C(6")], 137.33 [C(4)], 140.34 [C(1")], 142.58 [br, C(8a)], 147.82 [C(6)], 155.46 [C(2)].

6-(3-Benzylpyrrolidin-1-yl)quinolin-2-amine (21x)



Using General Method 11, **84x** (41 mg, 0.13 mmol) was reacted with LiHMDS solution (1.0 M in THF, 280 μL, 0.28 mmol), $Pd(dba)_2$ (0.7 mg, 1.3 μmol) and DavePhos (0.6 mg, 1.5 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 4% methanol in dichloromethane with 0.001% triethylamine gave **21x** as a yellow oil (27 mg, 70%). R_f = 0.19 (1:9 methanol/dichloromethane). MP: 145-148°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{20}H_{21}N_3$: 304.1814; found 304.1809. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.79 [1H, qd, $^2J_{4'a,4'b}$ = 12.3 Hz, $^3J_{3',4'a}$ = $^3J_{4'a,5'a}$ = $^3J_{4'a,5'b}$ = 8.0 Hz, H(4'$_a$)], 2.10-2.19 [1H, m, H(4'$_b$)], 2.64 [1H, septet, $^3J_{2'a,3'}$ = $^3J_{2'b,3'}$ = $^3J_{3',4'a}$ = $^3J_{3',4'b}$ = $^3J_{3',A}$ = $^3J_{3',A'}$ = 8.0 Hz, H(3')], 2.74-2.84 [2H, m, H(A) + H(A')], 3.08 [1H, t, $^2J_{2'a,2'b}$ = $^3J_{2'a,3'}$ = 8.0 Hz, H(2'$_a$)], 3.36 [1H, q, $^2J_{5'a,5'b}$ = $^3J_{4'a,5'a}$ = $^3J_{4'b,5'a}$ = 8.0 Hz, H(5'$_a$)], 3.41-3.51 [2H, m, H(2'$_b$) + H(5'$_b$)], 4.78 [2H, br s, NH_2], 6.55 [1H, d, $^4J_{5,7}$ = 2.6 Hz, H(5)], 6.67 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 7.02 [1H, dd, $^3J_{7,8}$ = 9.1 Hz, $^4J_{5,7}$ = 2.6 Hz, H(7)], 7.18-7.28 [3H, m, H(2") + H(4") + H(6")], 7.28-7.36 [2H, m, H(3") + H(5")], 7.56 [1H, d, $^3J_{7,8}$ = 9.1 Hz, H(8)], 7.74 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.63 [C(4')], 40.10 [C(A)], 40.69 [C(3')], 47.81 [C(5')], 53.56 [C(2')], 105.17 [C(5)], 112.20 [C(3)], 118.52 [C(7)], 124.95 [C(4a)], 126.16 [C(8)], 126.29 [C(4")], 128.61 [C(3") + C(5")], 128.87 [C(2") + C(6")], 137.19 [C(4)], 139.22 [br, C(8a)], 140.81 [C(1")], 144.23 [C(6)], 153.96 [C(2)].

6-(4-(Pyridin-2-ylmethyl)piperidin-1-yl)quinolin-2-amine (22a)

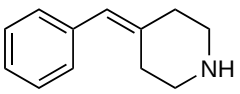


Using General Method 11, **85a** (64 mg, 0.19 mmol) was reacted with LiHMDS solution (1.0 M in THF, 419 μL, 0.42 mmol), $Pd(dba)_2$ (1.1 mg, 1.9 μmol) and DavePhos (0.9 mg, 2.3 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica

gel eluting with 7% methanol in dichloromethane gave **22a** as a yellow solid (32 mg, 53%). R_f = 0.36 (1:9 methanol/dichloromethane). MP: 182-184°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{20}H_{22}N_4$: 319.1923; found 319.1916. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ = 12.4 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.6 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.79 [2H, br d‡, $^2J_{(3'/5')ax,(3'/5')eq}$ = 12.4 Hz, H(3'$_{eq}$) + H(5'$_{eq}$)], 1.98 [1H, ttt, $^3J_{(3'/5')ax,4'ax}$ = 12.4 Hz, $^3J_{4'ax,A}$ = 7.1 Hz, $^3J_{(3'/5')eq,4'ax}$ = 3.6 Hz, H(4'$_{ax}$)], 2.71 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax}$ = 12.4 Hz, $^3J_{(2'/6')ax,(3'/5')eq}$ = 2.3 Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 2.78 [2H, d, $^3J_{4'ax,A}$ = 7.1 Hz, H(A)], 3.68 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.4 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 4.77 [2H, br s, NH_2], 6.67 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.98 [1H, d, $^4J_{5,7}$ = 2.7 Hz, H(5)], 7.10-7.18 [2H, m, H(4") + H(6")], 7.36 [1H, dd, $^3J_{7,8}$ = 9.2 Hz, $^4J_{5,7}$ = 2.7 Hz, H(7)], 7.57 [1H, d, $^3J_{7,8}$ = 9.2 Hz, H(8)], 7.61 [1H, td, $^3J_{4",5"} = {}^3J_{5",6"}$ = 7.7 Hz, $^4J_{3",5"}$ = 1.8 Hz, H(5")], 7.76 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)], 8.57 [1H, br d‡, $^3J_{3",4"}$ = 4.9 Hz, H(3")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.28 [C(3') + C(5')], 36.69 [C(4')], 45.44 [C(A)], 50.89 [C(2') + C(6')], 111.37 [C(5)], 111.88 [C(3)], 121.26 [C(4")], 123.78 [C(6")], 123.84 [C(7)], 124.30 [C(4a)], 126.35 [C(8)], 136.30 [C(5")], 137.63 [C(4)], 142.13 [br, C(8a)], 147.85 [C(6)], 149.56 [C(3")], 155.38 [C(2)], 160.62 [C(1")].

6.2.7 Synthesis of 2-aminoquinolines via benzylidenepiperidines

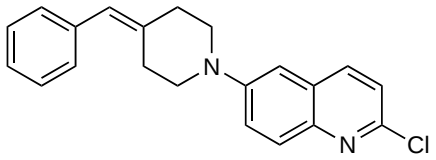
4-Benzylidenepiperidine (103x)



Hydrogen chloride solution (1M in diethyl ether, 3 mL) was added dropwise to a stirring suspension of **45x** (134 mg, 0.49 mmol) in diethyl ether (1 mL) and the mixture was stirred for 1 hr. The precipitate was collected by vacuum filtration, washed with ice-cold diethyl ether, then added to saturated aqueous sodium bicarbonate solution (30 mL) and stirred for 30 min. The mixture was extracted with dichloromethane (3 x 30 mL), dried over $MgSO_4$, filtered, and concentrated to dryness under reduced pressure to give **103x** as a colourless oil (68 mg, 80%) which was used without further purification. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{12}H_{15}N$: 174.1283; found 174.1278. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.97 [1H, br s, NH], 2.26-2.37 [2H, m, H(5')], 2.42-2.49 [2H, m, H(3')], 2.78-2.90 [2H, m, H(2')], 2.91-3.04 [2H, m, H(6')], 6.29 [1H, s, H(A)], 7.15-7.23 [3H, m, H(2') + H(4') + H(6')], 7.27-7.34 [2H, m, H(3') + H(5')].

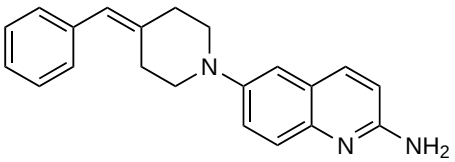
This data is consistent with that reported previously.[132]

6-(4-Benzylidenepiperidin-1-yl)-2-chloroquinoline (106x)



Using General Method 10, **103x** (68 mg, 0.39 mmol) and **24** (113 mg, 0.47 mmol) were reacted with $Pd(OAc)_2$ (0.4 mg, 1.8 μmol), CataCXium® A ligand (1.4 mg, 3.9 μmol) and sodium *tert*-butoxide (49 mg, 0.51 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **106x** as a yellow oil (84 mg, 64%). R_f = 0.63 (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{19}{}^{35}ClN_2/C_{21}H_{19}{}^{37}ClN_2$: 335.1315/337.1286; found 335.1308/337.1286. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.53-2.60 [2H, m, H(5')], 2.66-2.73 [2H, m, H(3')], 3.33-3.41 [2H, m, H(2')], 3.45-3.52 [2H, m, H(6')], 6.42 [1H, s, H(A)], 7.01 [1H, d, $^4J_{5,7}$ = 2.7 Hz, H(5)], 7.19-7.30 [4H, m, H(3) + H(2") + H(4") + H(6")], 7.31-7.38 [2H, m, H(3") + H(5")], 7.51 [1H, dd, $^3J_{7,8}$ = 9.3 Hz, $^4J_{5,7}$ = 2.7 Hz, H(7)], 7.88 [1H, d, $^3J_{7,8}$ = 9.3 Hz, H(8)], 7.91 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.98 [C(3')], 35.91 [C(5')], 50.25 [C(2')], 51.12 [C(6')], 108.97 [C(5)], 122.52 [C(3)], 123.52 [C(7)], 124.45 [C(A)], 126.50 [C(4")], 128.33 [C(4a)], 128.36 [C(3") + C(5")], 129.05 [C(2") + C(6")], 129.33 [C(8)], 137.49 [C(4)], 137.62 [C(4')], 138.35 [C(1")], 143.04 [C(8a)], 147.43 [C(2)], 149.48 [C(6)].

6-(4-Benzylidenepiperidin-1-yl)quinolin-2-amine (102x)

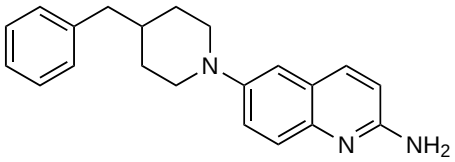


Using General Method 11, **106x** (74 mg, 0.22 mmol) was reacted with LiHMDS solution (1.0 M in THF, 488 μL, 0.49 mmol), $Pd(dba)_2$ (1.3 mg, 2.3 μmol) and DavePhos (1.0 mg, 2.5 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 2% methanol in dichloromethane with 0.001% triethylamine gave **102x** as a yellow oil (28 mg, 40%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{21}N_3$: 316.1814; found 316.1810. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.51-2.61 [2H, m, H(5')], 2.64-2.76 [2H, m, H(3')], 3.20-3.30 [2H, m, H(2')], 3.31-3.41 [2H, m, H(6')], 4.71 [2H, br s, NH_2], 6.39 [1H, s, H(A)], 6.68 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.98 [1H, d, $^4J_{5,7}$ = 2.6 Hz, H(5)], 7.19-7.29 [3H, m, H(2") + H(4") + H(6")], 7.28-7.37 [2H, m, H(3") + H(5")], 7.39 [1H, dd, $^3J_{7,8}$ = 9.2 Hz, $^4J_{5,7}$ = 2.6 Hz, H(7)], 7.59 [1H, d, $^3J_{7,8}$ = 9.2 Hz, H(8)], 7.77 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 29.25 [C(3')], 36.35 [C(5')], 51.58 [C(2')], 52.41 [C(6')], 111.53 [C(5)], 111.94 [C(3)], 123.66 [C(7)], 124.02 [C(A)], 124.37 [C(4a)], 126.39 [C(4")], 126.61

[C(8)], 128.32 [C(3") + C(5")], 129.10 [C(2") + C(6")], 137.57 [C(4)], 137.81 [C(1")], 138.95 [C(4')], *142.29 [C(8a)], 147.24 [C(6)], 155.44 [C(2)].

*The C(8a) signal was not observed in the ^{13}C NMR spectrum, and the chemical shift was instead determined using clear [^{1}H,^{13}C]-HMBC spectrum correlations with the H(4), H(5) and H(7) signals.

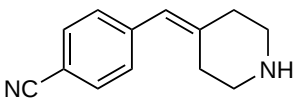
2-Amino-6-(4-benzylpiperidin-1-yl)quinoline (183)



Using General Method 3, **102x** (20 mg, 0.06 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 2 hr. Work-up and column chromatography on silica gel eluting with 10% methanol in dichloromethane gave **15** as a tan solid (18 mg, 91%). R_f = 0.21 (1:9 methanol/dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{23}N_3$: 318.1970; found 318.1966. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 [2H, qd, $^{2}J_{(3'/5')ax,(3'/5')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax} = {}^{3}J_{(3'/5')ax,4'ax}$ = 12.2 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.8 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.70 [1H, ttt, $^{3}J_{(3'/5')ax,4'ax}$ = 12.2 Hz, $^{3}J_{4'ax,A}$ = 7.3 Hz, $^{3}J_{(3'/5')eq,4'ax}$ = 3.8 Hz, H(4'$_{ax}$)], 1.79 [2H, br d‡, $^{2}J_{(3'/5')ax,(3'/5')eq}$ = 12.2 Hz, H(3'$_{eq}$) + H(5'$_{eq}$)], 2.61 [2H, d, $^{3}J_{4'ax,A}$ = 7.3 Hz, H(A)], 2.67 [2H, td, $^{2}J_{(2'/6')ax,(2'/6')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax}$ = 12.2 Hz, $^{3}J_{(2'/6')ax,(3'/5')eq}$ = 2.2 Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 3.68 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.2 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 4.73 [2H, br s, NH_2], 6.67 [1H, d, $^{3}J_{3,4}$ = 8.8 Hz, H(3)], 6.96 [1H, d, $^{4}J_{5,7}$ = 2.6 Hz, H(5)], 7.14-7.24 [3H, m, H(2") + H(4") + H(6")], 7.27-7.33 [2H, m, H(3") + H(5")], 7.36 [1H, dd, $^{3}J_{7,8}$ = 9.2 Hz, $^{4}J_{5,7}$ = 2.6 Hz, H(7)], 7.57 [1H, d, $^{3}J_{7,8}$ = 9.2 Hz, H(8)], 7.76 [1H, d, $^{3}J_{3,4}$ = 8.8 Hz, H(4)].

This data is consistent with that reported previously.[52]

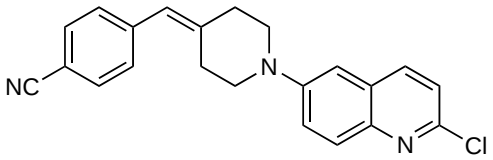
4-(Piperidin-4-ylidenemethyl)benzonitrile (103s)



Using General Method 4, **45s** (394 mg, 1.32 mmol) was reacted with trifluoroacetic acid (1.5 mL) in dichloromethane (5 mL) for 1 hr, to give **103s** as a pale yellow oil (264 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{13}H_{14}N_2$: 199.1235; found 199.1236. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34-2.45 [2H, m, H(5)], 2.45-2.55 [2H, m, H(3)], 2.85-2.97 [2H, m, H(2)], 2.98-3.09 [2H, m, H(6)], 3.26 [1H, br s, NH], 6.31 [1H, s, H(A)], 7.24-7.33 [2H, m, H(2') + H(6')], 7.55-7.64 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.22 [C(3)],

37.32 [C(5)], 47.13 [C(2)], 47.88 [C(6)], 109.84 [C(4')], 119.15 [CN], 122.71 [C(A)], 129.61 [C(2') + C(6')], 132.10 [C(3') + C(5')], 142.28 [C(1')], 142.41 [C(4)].

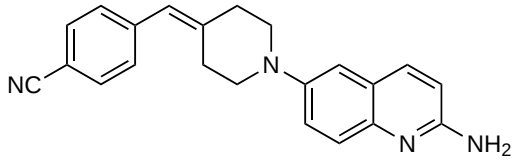
4-((1-(2-Chloroquinolin-6-yl)piperidin-4-ylidene)methyl)benzonitrile (106s)



Synthesis method a. Using General Method 10, **103s** (110 mg, 0.55 mmol) and **24** (161 mg, 0.66 mmol) were reacted with $Pd(OAc)_2$ (0.6 mg, 2.4 μmol), CataCXium® A ligand (2.0 mg, 5.6 μmol) and sodium *tert*-butoxide (69 mg, 0.72 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with 1% methanol in dichloromethane gave **106s** as a yellow oil (70 mg, 35%). R_f = 0.22 (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{18}{}^{35}ClN_3/C_{22}H_{18}{}^{37}ClN_3$: 360.1268/362.1238; found 360.1260/362.1239. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.55-2.63 [2H, m, H(5')], 2.63-2.71 [2H, m, H(3')], 3.34-3.43 [2H, m, H(2')], 3.46-3.54 [2H, m, H(6')], 6.41 [1H, s, H(A)], 7.02 [1H, d, $^4J_{5,7}$ = 2.7 Hz, H(5)], 7.28 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(3)], 7.30-7.36 [2H, m, H(2'') + H(6'')], 7.51 [1H, dd, $^3J_{7,8}$ = 9.3 Hz, $^4J_{5,7}$ = 2.7 Hz, H(7)], 7.59-7.66 [2H, m, H(3'') + H(5'')], 7.89 [1H, d, $^3J_{7,8}$ = 9.3 Hz, H(8)], 7.91 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 29.12 [C(3')], 36.01 [C(5')], 50.06 [C(2')], 50.97 [C(6')], 109.12 [C(5)], 110.03 [C(4'')], 119.14 [CN], 122.61 [C(3)], 123.14 [C(A)], 123.45 [C(7)], 128.27 [C(4a)], 129.45 [C(8)], 129.65 [C(2'') + C(6'')], 132.19 [C(3'') + C(5'')], 137.50 [C(4)], 141.86 [C(4')], 142.36 [C(1'')], 143.13 [C(8a)], 147.61 [C(6)], 149.18 [C(2)].

Synthesis method b. A mixture of **103s** (150 mg, 0.76 mmol) and **24** (220 mg, 0.91 mmol) were combined in a glass pressure tube with $Pd(OAc)_2$ (0.8 mg, 3.6 μmol), CataCXium® A ligand (2.7 mg, 7.5 μmol) and sodium *tert*-butoxide (95 mg, 0.98 mmol). 1,4-dioxane (2 mL) was added and the tube was sealed and heated to 90°C for 16 hr. The mixture was cooled, diluted with methanol (5 mL) and filtered through Celite®, washing with methanol. The solvent was removed by evaporation under reduced pressure and the residue was purified by column chromatography on silica gel eluting with 1% methanol in dichloromethane to give **106s** as a yellow oil (101 mg, 37%). Data as above.

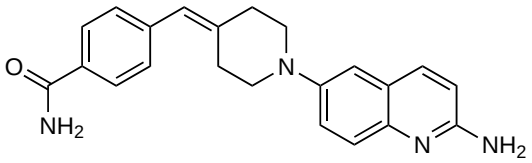
4-((1-(2-Aminoquinolin-6-yl)piperidin-4-ylidene)methyl)benzonitrile (102s)



Using General Method 11, **106s** (32 mg, 0.09 mmol) was reacted with LiHMDS solution (1.0 M in THF, 195 μL, 0.20 mmol), $Pd(dba)_2$ (0.5 mg, 0.9 μmol) and DavePhos (0.4 mg, 1.1 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 5% methanol in dichloromethane with 0.001% triethylamine gave **102s** as a yellow oil (23 mg, 77%). R_f = 0.10 (1:19 methanol/dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{20}N_4$: 341.1766; found 341.1764. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.55-2.62 [2H, m, H(5')], 2.63-2.72 [2H, m, H(3')], 3.22-3.30 [2H, m, H(2')], 3.33-3.43 [2H, m, H(6')], 4.70 [2H, br s, NH_2], 6.38 [1H, s, H(A)], 6.69 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.98 [1H, d, $^4J_{5,7}$ = 2.3 Hz, H(5)], 7.29-7.35 [2H, m, H(2'') + H(6'')], 7.38 [1H, dd, $^3J_{7,8}$ = 9.1 Hz, $^4J_{5,7}$ = 2.3 Hz, H(7)], 7.56-7.66 [3H, m, H(8) + H(3'') + H(5'')], 7.77 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 29.37 [C(3')], 36.45 [C(5')], 51.40 [C(2')], 52.26 [C(6')], 109.88 [C(4'')], 111.66 [C(5)], 112.04 [C(3)], 119.21 [CN], 122.71 [C(A)], 123.54 [C(7)], 124.32 [C(4a)], 126.77 [C(8)], 129.68 [C(2'') + C(6'')], 132.16 [C(3'') + C(5'')], 137.46 [C(4)], 142.51 [*C(4')], 142.57 [*C(1'')], 142.59 [*C(8a)], 146.83 [C(6)], 155.60 [C(2)].

*Some ^{13}C NMR signals could not be unambiguously assigned due to close proximity of chemical shifts.

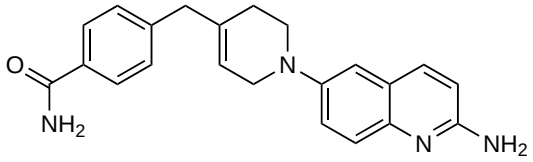
4-((1-(2-Aminoquinolin-6-yl)piperidin-4-ylidene)methyl)benzamide (104)



A sample of **102s** (32 mg, 0.09 mmol) was dissolved in ethanol (4 mL) with water (1 drop). Potassium hydroxide pellets (28 mg, 0.47 mmol) were added over 10 minutes. The mixture was stirred at room temperature for 30 min then 70°C for 2 hr, before cooling to 60°C and adding ice water (10 mL). The mixture was stirred at 0°C for 30 min and no precipitate was formed. The ethanol was removed by evaporation under reduced pressure and mixture extracted with ethyl acetate. The volatile solvent was removed by evaporation under reduced pressure and the residue was purified by column chromatography on silica gel eluting with 10% methanol in dichloromethane. A small amount (7 mg) of a mixture of products was

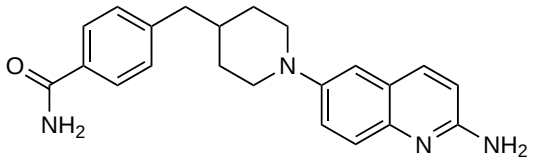
obtained, with ^{1}H NMR analysis indicating that the mixture contained predominantly **104** and 4-((1-(2-aminoquinolin-6-yl)-1,2,3,6-tetrahydropyridin-4-yl)methyl)benzamide (**105**). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{22}N_4O$: 359.1872; found 359.1865. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.20 [0.4H, br s‡, *H(5')], 2.54-2.62 [1.6H, m, H(5')], 2.65-2.72 [1.6H, m, H(3')], 3.21-3.30 [1.6H, m, H(2')], 3.33-3.40 [2H, m, H(6') + *H(6')], 3.43 [0.4H, br s, *H(A)], 3.75 [0.4H, br s‡, *H(2')], 4.96-5.18 [2H, br s, NH_2 + *NH_2], 5.47-6.16 [2.4H, m, $CONH_2$ + *$CONH_2$ + *H(3')], 6.41 [0.8H, s, H(A)], 6.67-6.72 [1H, m, H(3) + *H(3)], 6.95 [0.2H, d, $^4J_{5,7}$ = 2.6 Hz, *H(5)], 6.99 [0.8H, d, $^4J_{5,7}$ = 2.6 Hz, H(5)], 7.27-7.34 [2H, m, H(2'') + H(6'') + *H(2'') + *H(6'')], 7.35-7.42 [1H, m, H(7) + *H(7)], 7.58-7.63 [1H, m, H(8) + *H(8)], 7.73-7.82 [3H, m, H(4) + H(3'') + H(5'') + *H(4) + *H(3'') + *H(5'')].

*Denotes signals corresponding to minor product **105**.



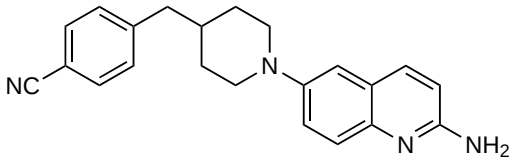
105

4-((1-(2-Aminoquinolin-6-yl)piperidin-4-yl)methyl)benzamide (101)



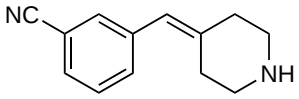
Using General Method 3, a mixture of **104** and **105** (7 mg, 20 μmol) was reacted with Pd-C catalyst under a hydrogen atmosphere for 2 hr. Work-up and column chromatography on silica gel eluting with 1:9 methanol/dichloromethane gave **101** as a white solid (6 mg, 85%). R_f = 0.15 (1:9 methanol/dichloromethane). MP: degraded 190°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{24}N_4O$: 361.2028; found 361.2024. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ = 12.0 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.3 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.63-1.83 [3H, m, H($3'_{eq}$) + H($4'_{ax}$) + H($5'_{eq}$)], 2.62-2.73 [4H, m, H($2'_{ax}$) + H($6'_{ax}$) + H(A)], 3.68 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.0 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 5.13 [2H, br s, NH_2], 5.54 [1H, br s, $CONH_2$], 6.01 [1H, br s, $CONH_2$], 6.67 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.98 [1H, d, $^4J_{5,7}$ = 2.7 Hz, H(5)], 7.22-7.31 [2H, m, H(2'') + H(6'')], 7.36 [1H, dd, $^3J_{7,8}$ = 9.2 Hz, $^4J_{5,7}$ = 2.7 Hz, H(7)], 7.59 [1H, d, $^3J_{7,8}$ = 9.2 Hz, H(8)], 7.72-7.81 [2H, m, H(3'') + H(5'')]. ^{13}C NMR (126 MHz, $(CD_3)_2CO$): δ 32.85 [C(3') + C(5')], 38.59 [C(4')], 43.44 [C(A)], 51.07 [C(2') + C(6')], 112.18 [C(5)], 113.28 [C(3)], 124.27 [C(7)], 124.27 [C(8)], 124.57 [C(4a)], 128.39 [C(3'') + C(5'')], 129.89 [C(2'') + C(6'')], 133.16 [C(4'')], 138.96 [C(4)], 145.15 [C(1'')], 148.64 [C(6)], 156.54 [C(2)], 169.02 [$CONH_2$].

4-((1-(2-Aminoquinolin-6-yl)piperidin-4-yl)methyl)benzonitrile (19s)



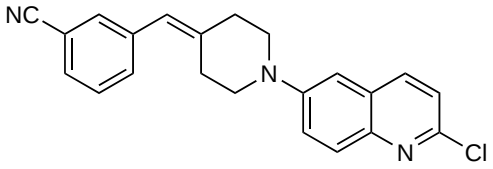
Using General Method 3, **102s** (25 mg, 0.07 mmol) was reacted with Pd-C catalyst in methanol (20 mL) under a hydrogen atmosphere for 2 hr. Work-up and column chromatography on silica gel eluting with 1:9 methanol/dichloromethane gave **19s** as a yellow solid (18 mg, 72%). R_f = 0.31 (1:9 methanol/dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{22}N_4$: 343.1923; found 343.1919. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ = 12.1 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.0 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.59-1.87 [3H, m, H(4'$_{ax}$) + H(3'$_{eq}$) + H(5'$_{eq}$)], 2.59-2.75 [4H, m, H(2'$_{ax}$) + H(6'$_{ax}$) + H(A)], 3.68 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.1 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 4.67 [2H, br s, NH_2], 6.68 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.96 [1H, d, $^4J_{5,7}$ = 2.0 Hz, H(5)], 7.26-7.32 [2H, m, H(2") + H(6")], 7.35 [1H, dd, $^3J_{7,8}$ = 9.2 Hz, $^4J_{5,7}$ = 2.0 Hz, H(7)], 7.53-7.64 [3H, m, H(8) + H(3") + H(5")], 7.76 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.18 [C(3') + C(5')], 37.76 [C(4')], 43.40 [C(A)], 50.84 [C(2') + C(6')], 110.09 [C(4")], 111.47 [C(5)], 111.94 [C(3)], 119.19 [CN], 123.76 [C(7)], 124.26 [C(4a)], 126.38 [C(8)], 130.04 [C(2") + C(6")], 132.28 [C(3") + C(5")], 137.68 [C(4)], 142.57 [C(8a)], 146.29 [C(1")], 147.68 [C(6)], 155.40 [C(2)].

3-(Piperidin-4-ylidenemethyl)benzonitrile (103r)



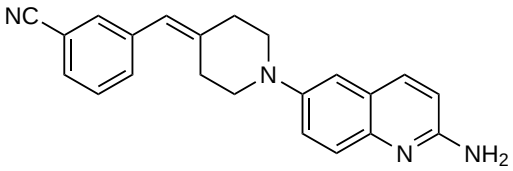
Using General Method 4, **45r** (44 mg, 0.15 mmol) and trifluoroacetic acid (0.5 mL) were reacted in dichloromethane (4 mL) to give **103r** as an orange oil (29 mg, 100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36-2.43 [2H, m, H(5)], 2.43.2.49 [2H, m, H(3)], 2.77-2.99 [3H, m, H(2) + NH], 2.99-3.06 [2H, m, H(6)], 6.28 [1H, s, H(A)], 7.39-7.51 [4H, m, H(2') + H(3') + H(5') + H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.14 [C(3)], 37.23 [C(5)], 47.20 [C(2)], 47.94 [C(6)], 112.47 [C(3')], 119.02 [CN], 121.91 [C(A)], 129.13 [C(5')], 129.91 [C(2')], 132.45 [C(4')], 133.42 [C(6')], 138.81 [C(1')], 141.69 [C(4)].

3-((1-(2-Chloroquinolin-6-yl)piperidin-4-ylidene)methyl)benzonitrile (106r)



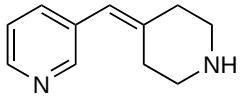
Using General Method 10, **103r** (90 mg, 0.45 mmol) and **24** (130 mg, 0.54 mmol) were reacted with $Pd(OAc)_2$ (0.5 mg, 2.2 μmol), CataCXium® A ligand (1.6 mg, 4.5 μmol) and sodium *tert*-butoxide (56 mg, 0.58 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with 1% methanol in dichloromethane gave **106r** as a yellow oil (103 mg, 63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.54-2.60 [2H, m, H(5')], 2.61-2.67 [2H, m, H(3')], 3.34-3.40 [2H, m, H(2')], 3.46-3.52 [2H, m, H(6')], 6.37 [1H, s, H(A)], 7.02 [1H, d, $^4J_{5,7} = 2.7$ Hz, H(5)], 7.28 [1H, d, $^3J_{3,4} = 8.6$ Hz, H(3)], 7.39-7.47 [2H, m, H(7) + H(4")], 7.48-7.54 [3H, m, H(2") + H(5") + H(6")], 7.88 [1H, d, $^3J_{7,8} = 9.3$ Hz, H(8)], 7.91 [1H, d, $^3J_{3,4} = 8.6$ Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.93 [C(3)], 35.82 [C(5)], 50.06 [C(2)], 50.97 [C(6)], 109.12 [C(5)], 112.54 [C(3")], 118.99 [CN], 122.34 [C(A)], 122.56 [C(3)], 123.47 [C(7)], 128.25 [C(4a)], 129.20 [C(5")], 129.38 [C(8)], 130.00 [C(2")], 132.43 [C(4")], 133.41 [C(6")], 137.51 [C(4)], 138.74 [C(1")], 141.12 [C(4')], 143.09 [C(8a)], 147.55 [C(6)], 149.20 [C(2)].

3-((1-(2-Aminoquinolin-6-yl)piperidin-4-ylidene)methyl)benzonitrile (102r)



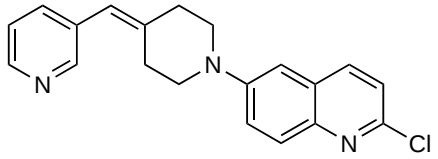
Using General Method 11, **106r** (93 mg, 0.26 mmol) was reacted with LiHMDS solution (1.0 M in THF, 570 μL, 0.57 mmol), $Pd(dba)_2$ (1.5 mg, 2.6 μmol) and DavePhos (1.2 mg, 3.0 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane/methanol with 0.001% triethylamine gave **102r** as a yellow oil (39 mg, 42%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{20}N_4$: 341.1766; found 341.1758. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.54-2.60 [2H, m, H(5')], 2.60-2.67 [2H, m, H(3')], 3.21-3.29 [2H, m, H(2')], 3.32-3.41 [2H, m, H(6')], 4.91 [2H, br s, NH_2], 6.35 [1H, s, H(A)], 6.70 [1H, d, $^3J_{3,4} = 8.8$ Hz, H(3)], 6.99 [1H, d, $^4J_{5,7} = 2.7$ Hz, H(5)], 7.39 [1H, dd, $^3J_{7,8} = 9.1$ Hz, $^4J_{5,7} = 2.7$ Hz, H(7)], 7.41-7.47 [2H, m, H(4") + H(5")], 7.48-7.54 [2H, m, H(2") + H(6")], 7.61 [1H, d, $^3J_{7,8} = 9.1$ Hz, H(8)], 7.79 [1H, d, $^3J_{3,4} = 8.8$ Hz, H(4)].

3-(Piperidin-4-ylidenemethyl)pyridine (110b)



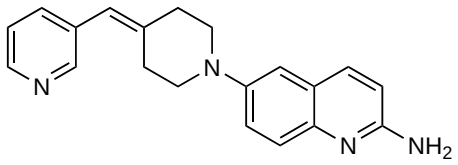
Using General Method 4, **53b** (200 mg, 0.73 mmol) was reacted with trifluoroacetic acid (2 mL) to give **110b**, which was used without further purification (25 mg, 20%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{11}H_{14}N_2$: 175.1235; found 175.1232. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.29-2.35 [2H, m, H(5)], 2.36-2.42 [2H, m, H(3)], 2.74-2.89 [3H, m, H(2) + NH], 2.90-2.98 [2H, m, H(6)], 6.17 [1H, s, H(A)], 7.17 [1H, dd, $^3J_{5',6'} = 7.8$ Hz, $^3J_{4',5'} = 4.8$ Hz, H(5')], 7.42 [1H, dt, $^3J_{5',6'} = 7.8$ Hz, $^4J_{2',6'} = {}^4J_{4',6'} = 1.6$ Hz, H(6')], 8.31-8.42 [2H, m, H(2') + H(4')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.93 [C(3)], 40.08 [C(5)], 49.93 [C(2)], 50.66 [C(6)], 122.60 [C(A)], 125.70 [C(5')], 135.88 [C(1')], 138.68 [C(6')], 144.53 [C(4)], 149.87 [C(4')], 152.61 [C(2')].

2-Chloro-6-(4-(pyridin-3-ylmethylene)piperidin-1-yl)quinoline (111b)



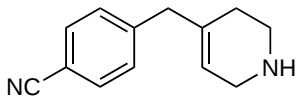
Using General Method 10, **110b** (25 mg, 0.14 mmol) and **24** (42 mg, 0.17 mmol) were reacted with $Pd(OAc)_2$ (0.2 mg, 0.9 μmol), CataCXium® A ligand (0.5 mg, 1.4 μmol) and sodium *tert*-butoxide (18 mg, 0.19 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with 1% methanol in dichloromethane gave **111b** as an orange oil (22 mg, 46%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{20}H_{18}{}^{35}ClN_3$/ $C_{20}H_{18}{}^{37}ClN_3$: 336.1268/338.1238; found 336.1260/338.1240. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.57-2.62 [2H, m, H(5')], 2.63-2.69 [2H, m, H(3')], 3.35-3.42 [2H, m, H(2')], 3.47-3.53 [2H, m, H(6')], 6.36 [1H, s, H(A)], 7.02 [1H, d, $^4J_{5,7} = 2.2$ Hz, H(5)], 7.24-7.31 [2H, m, H(3) + H(5'')], 7.48-7.57 [2H, m, H(7) + H(6'')], 7.89 [1H, d, $^3J_{7,8} = 9.3$ Hz, H(8)], 7.92 [1H, d, $^3J_{3,4} = 8.6$ Hz, H(4)], 8.47 [1H, br d‡, $^3J_{4'',5''} = 4.7$ Hz, H(4'')], 8.51 [1H, br s‡, H(2'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.98 [C(3')], 35.93 [C(5')], 50.19 [C(2')], 51.05 [C(6')], 109.12 [C(5)], 120.78 [C(A)], 122.58 [C(3)], 123.26 [C(5'')], 123.51 [C(7)], 128.29 [C(4a)], 129.41 [C(8)], 133.25 [C(1'')], 136.13 [C(6'')], 137.51 [C(4)], 141.06 [C(4')], 143.12 [C(8a)], 147.56 [C(2)], 147.61 [C(4'')], 149.30 [C(6)], 150.16 [C(2'')].

6-(4-(Pyridin-3-ylmethylene)piperidin-1-yl)quinolin-2-amine (108b)



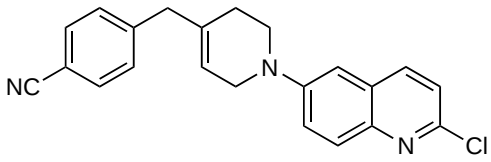
Using General Method 11, **111b** (22 mg, 0.07 mmol) was reacted with LiHMDS solution (1.0 M in THF, 144 μL, 0.14 mmol), $Pd(dba)_2$ (0.4 mg, 0.7 μmol) and DavePhos (0.3 mg, 0.8 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 3% methanol in dichloromethane with 0.001% triethylamine gave **108b** as a yellow oil (11 mg, 53%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{20}H_{20}N_4$: 317.1766; found 317.1760. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.53-2.61 [2H, m, H(5')], 2.62-2.70 [2H, m, H(3')], 3.20-3.30 [2H, m, H(2')], 3.34-3.42 [2H, m, H(6')], 5.19 [2H, br s, NH_2], 6.33 [1H, s, H(A)], 6.70 [1H, d, $^3J_{3,4} = 8.8$ Hz, H(3)], 6.98 [1H, d, $^4J_{5,7} = 2.7$ Hz, H(5)], 7.24-7.29 [1H, m, H(5'')], 7.39 [1H, dd, $^3J_{7,8} = 9.1$ Hz, $^4J_{5,7} = 2.7$ Hz, H(7)], 7.54 [1H, br d, $^3J_{5'',6''} = 7.9$ Hz, H(6'')], 7.61 [1H, d, $^3J_{7,8} = 9.1$ Hz, H(8)], 7.79 [1H, d, $^3J_{3,4} = 8.8$ Hz, H(4)], 8.46 [1H, br d‡, $^3J_{4'',5''} = 4.0$ Hz, H(4'')], 8.51 [1H, br s‡, H(2'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 29.20 [C(3')], 36.31 [C(5')], 51.40 [C(2')], 52.22 [C(6')], 111.65 [C(5)], 112.22 [C(3)], 120.39 [C(A)], 123.23 [C(5'')], 123.70 [C(7)], 124.07 [C(4a)], 125.84 [C(8)], 133.39 [C(1'')], 136.16 [C(6'')], 138.02 [C(4)], 141.22 [br, C(8a)], 141.59 [C(4')], 147.13 [C(6)], 147.50 [C(4'')], 150.20 [C(2'')], 155.41 [C(2)].

4-((1,2,3,6-Tetrahydropyridin-4-yl)methyl)benzonitrile (112s)



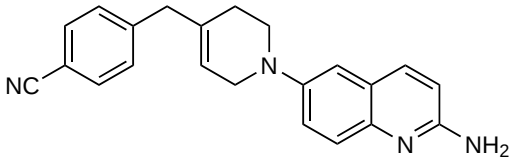
Using General Method 4, **55s** (219 mg, 0.73 mmol) was reacted with trifluoroacetic acid (2 mL) for 1 hr. Work-up followed by purification by column chromatography on silica gel eluting with dichloromethane gave **112s** as a red oil (59 mg, 41%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{13}H_{14}N_2$: 199.1235; found 199.1229. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.25 [2H, br s‡, H(5)], 3.21 [2H, t, $^3J_{5,6} = 6.0$ Hz, H(6)], 3.42 [2H, s, H(A)], 3.62 [2H, br s‡, H(2)], 5.44 [1H, br s‡, H(3)], 6.44 [1H, br s, NH], 7.26-7.32 [2H, m, H(2') + H(6')], 7.55-7.63 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.17 [C(5)], 40.92 [C(6)], 41.96 [C(2)], 43.47 [C(A)], 110.90 [C(4')], 117.28 [C(3)], 118.87 [CN], 129.91 [C(2') + C(6')], 132.56 [C(3') + C(5')], 135.98 [C(4)], 143.46 [C(1')].

4-((1-(2-Chloroquinolin-6-yl)-1,2,3,6-tetrahydropyridin-4-yl)methyl)benzonitrile (107s)



Using General Method 10, **112s** (45 mg, 0.23 mmol) and **24** (66 mg, 0.27 mmol) were reacted with $Pd(OAc)_2$ (0.3 mg, 1.1 μmol), CataCXium® A ligand (0.8 mg, 2.3 μmol) and sodium *tert*-butoxide (28 mg, 0.30 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave a crude mixture containing largely **184s** as a red oil (38 mg, 47%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.19 [2H, br s‡, H(5')], 3.44 [2H, br s, H(A)], 3.48 [2H, t, $^3J_{5',6'}$ = 5.7 Hz, H(6')], 3.83 [2H, br s‡, H(2')], 5.59 [1H, br s‡, H(3')], 6.95 [1H, d, $^4J_{5,7}$ = 2.5 Hz, H(5)], 7.27 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(3)], 7.29-7.35 [2H, m, H(2") + H(6")], 7.47 [1H, dd, $^3J_{7,8}$ = 9.3 Hz, $^4J_{5,7}$ = 2.5 Hz, H(7)], 7.57-7.63 [2H, m, H(3") + H(5")], 7.87 [1H, d, $^3J_{7,8}$ = 9.3 Hz, H(8)], 7.90 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.84 [C(5')], 43.69 [C(A)], 45.59 [C(6')], 48.04 [C(2')], 107.81 [C(5)], 110.46 [C(4")], 119.07 [CN], 121.33 [C(3')], 122.26 [C(7)], 122.55 [C(3)], 128.31 [C(4a)], 129.30 [C(8)], 129.90 [C(2") + C(6")], 132.40 [C(3") + C(5")], 135.23 [C(4')], 137.45 [C(4)], 142.82 [C(8a)], 144.89 [C(1")], 147.25 [C(2)], 148.98 [C(6)].

4-((1-(2-Aminoquinolin-6-yl)-1,2,3,6-tetrahydropyridin-4-yl)methyl)benzonitrile (109s)



Using General Method 11, **184s** (28 mg, 0.08 mmol) was reacted with LiHMDS solution (1.0 M in THF, 170 μL, 0.17 mmol), $Pd(dba)_2$ (0.5 mg, 0.8 μmol) and DavePhos (0.3 mg, 0.9 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 1% methanol in dichloromethane gave an inseparable mixture of **109s** and **19s** as a red oil (11 mg). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{20}N_4$: 341.1766; found 341.1758. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{22}N_4$: 343.1923; found 343.1913. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [0.8H, qd, $^2J_{(*3'/*5')ax,(*3'/*5')eq}$ = $^3J_{(*2'/*6')ax,(*3'/*5')ax}$ = $^3J_{(*3'/*5')ax,*4'ax}$ = 12.1 Hz, $^3J_{(*2'/*6')eq,(*3'/*5')ax}$ = 3.0 Hz, *H($3'_{ax}$) + *H($5'_{ax}$)], 1.59-1.87 [1.2H, m, *H($4'_{ax}$) + *H($3'_{eq}$) + *H($5'_{eq}$)], 2.18 [1.2H, br s‡, H(5')], 2.61-2.74 [1.6H, m, *H($2'_{ax}$) + *H($6'_{ax}$) + *H(A)], 3.37 [1.2H, t, $^3J_{5',6'}$ = 5.7 Hz, H(6')], 3.43 [1.2H, s, H(A)],

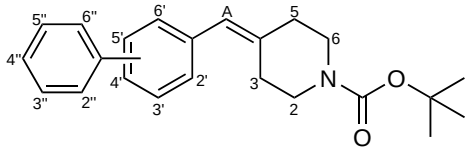
3.68 [0.8H, br d‡, $^{2}J_{(*2'/*6')ax,(*2'/*6')eq}$ = 12.1 Hz, *H($2'_{eq}$) + *H($6'_{eq}$)], 3.75 [1.2H, br s‡, H(2')], 4.72 [2H, br s, NH_2 + *NH_2], 5.58 [0.6H, br s‡, H(3')], 6.64-6.72 [1H, m, H(3) + *H(3)], 6.90-6.98 [1H, m, H(5) + *H(5)], 7.27-7.39 [3H, m, H(7) + H(2'') + H(6'') + *H(7) + *H(2'') + *H(6'')], 7.53-7.65 [3H, m, H(8) + H(3'') + H(5'') + *H(8) + *H(3'') + *H(5'')], 7.73-7.81 [1H, m, H(4) + *H(4)].

*Denotes signals corresponding to minor product **19s**.

6.3 2-Aminoquinolines with 6-position biaryl substituents

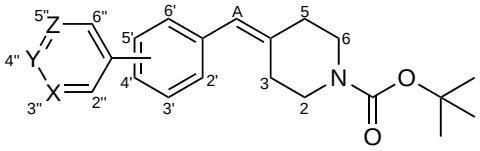
6.3.1 Synthesis of biaryl-extended 4-piperidine derivatives

General Method 12: Suzuki reaction for synthesis of biphenyl compounds



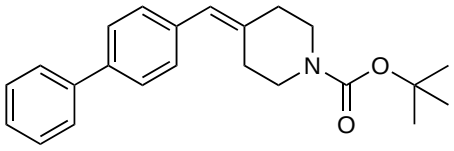
A mixture of the aryl bromide (1.0 eq) and phenylboronic acid (1.2 eq) was combined with $Pd(OAc)_2$ (3 mol %), PPh_3 (5 mol %) and potassium carbonate (1.5 eq) in toluene in a glass pressure tube. The tube was sealed and heated at 100°C for the given time, then cooled and filtered through Celite® washing with methanol. The solvent was removed by evaporation under reduced pressure and purified by column chromatography with the specified eluant.

General Method 13: Suzuki reaction for synthesis of biaryl compounds



A mixture of the aryl bromide (1.0 eq) and arylboronic acid derivative (1.2 eq) was combined with $Pd(OAc)_2$ (3 mol %), PPh_3 (5 mol %) and potassium carbonate (1.5 eq) in toluene/ ethanol (1:1) in a glass pressure tube. The tube was sealed and heated at 100°C for the given time, then cooled and filtered through Celite® washing with methanol. The solvent was removed by evaporation under reduced pressure and purified by column chromatography with the specified eluant.

***tert*-Butyl 4-((1,1'-biphenyl)-4-ylmethylene)piperidine-1-carboxylate (121b)**



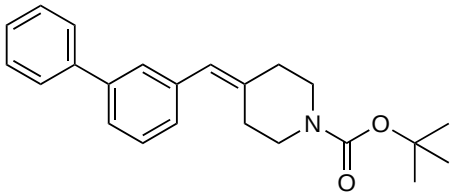
Synthesis method a.[133] A mixture of **45m** (100 mg, 0.28 mmol), phenylboronic acid (52 mg, 0.43 mmol), $Pd(PPh_3)_4$ (9.8 mg, 8.5 μmol), and potassium carbonate (59 mg, 0.43 mmol) in toluene (2.5 mL) were combined in a glass pressure tube in toluene (2 mL). The tube was sealed and heated to 80°C for 2 hr, then cooled, quenched with water, and extracted

with dichloromethane (3 x 30 mL). Removal of volatile solvent under reduced pressure gave a crude residue. ^{1}H NMR analysis demonstrated the mixture contained a 3:1 mixture of starting material **45m** and target product **121b**.

Synthesis method b.[92] A mixture of **45m** (100 mg, 0.28 mmol), phenylboronic acid (52 mg, 0.43 mmol), $Pd(OAc)_2$ (0.6 mg, 2.7 μmol), and sodium carbonate (60 mg, 0.57 mmol) in toluene (2.5 mL) were combined in H_2O/DMF (3.5:3, 3 mL) and heated to 35°C for 2 hr, then cooled, quenched with water, and extracted with dichloromethane (3 x 30 mL). Removal of volatile solvent under reduced pressure gave a crude residue containing only unreacted starting material.

Synthesis method c. Using General Method 12, **45m** (400 mg, 1.14 mmol) and phenylboronic acid (208 mg, 1.71 mmol) were reacted in a glass pressure tube with $Pd(OAc)_2$ (7.6 mg, 32 μmol), PPh_3 (15 mg, 57 μmol) and potassium carbonate (235 mg, 1.70 mmol) in toluene (2.5 mL) for 4 hr. The residue was purified by column chromatography on silica gel eluting with 1:19 ethyl acetate/hexane to give **121b** as a white solid (288 mg, 73%). $R_f = 0.24$ (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{23}H_{27}NO_2 - C(CH_3)_3$: 294.1494; found 294.1488. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.30-2.40 [2H, m, H(5)], 2.47-2.57 [2H, m, H(3)], 3.37-3.47 [2H, m, H(2)], 3.49-3.57 [2H, m, H(6)], 6.39 [1H, s, H(A)], 7.24-7.30 [2H, m, H(2') + H(6')], 7.33 [1H, br t‡, $^3J_{3'',4''} = {}^3J_{4'',5''} = 7.4$ Hz, H(4'')], 7.40-7.47 [2H, m, H(3'') + H(5'')], 7.53-7.57 [2H, m, H(3') + H(5')], 7.57-7.62 [2H, m, H(2'') + H(6'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.59 [^{t}Bu], 29.43 [br, C(3)], 36.41 [br, C(5)], 45.17 [br, C(2) + C(6)], 79.67 [^{t}Bu], 124.27 [C(A)], 126.98 [C(3') + C(5')], 127.06 [C(2'') + C(6'')], 127.32 [C(4'')], 128.88 [C(3'') + C(5'')], 129.43 [C(2') + C(6')], 136.58 [C(1)], 138.84 [C(4)], 139.23 [C(4')], 140.90 [C(1'')], 154.88 [C=O].

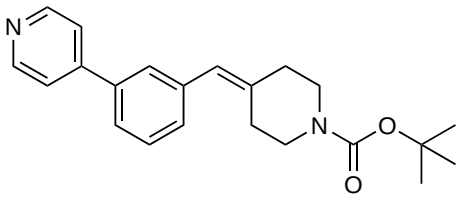
tert-Butyl 4-((1,1'-biphenyl)-3-ylmethylene)piperidine-1-carboxylate (121a)



Using General Method 12, **45l** (278 mg, 0.79 mmol), phenylboronic acid (149 mg, 1.22 mmol), $Pd(OAc)_2$ (5.3 mg, 24 μmol), PPh_3 (10 mg, 38 μmol) and potassium carbonate (164 mg, 1.19 mmol) in toluene (2.5 mL) were reacted for 4 hr. Work-up as specified and column chromatography on silica gel eluting with 1:19 ethyl acetate/hexane gave **121a** as a pale yellow oil (223 mg, 81%). $R_f = 0.20$ (1:9 ethyl acetate/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.30-2.42 [2H, m, H(5)], 2.46-2.58 [2H, m, H(3)], 3.36-3.47 [2H, m, H(2)], 3.48-3.58 [2H, m, H(6)], 6.42 [1H, s, H(A)], 7.18 [1H, br d‡, $^3J_{5',6'} = 7.5$ Hz,

H(6')], 7.32-7.48 [6H, m, H(2') + H(4') + H(5') + H(3") + H(4") + H(5")], 7.55-7.62 [2H, m, H(2") + H(6")].

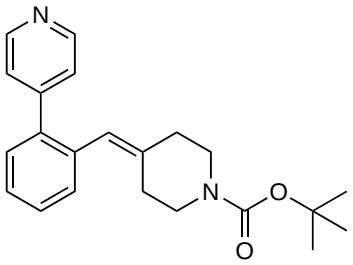
***tert*-Butyl 4-(3-(pyridin-4-yl)benzylidene)piperidine-1-carboxylate (122b)**



Synthesis method a. Using General Method 12, **45l** (104 mg, 0.30 mmol), 4-pyridinylboronic acid (73 mg, 0.59 mmol), $Pd(OAc)_2$ (2.0 mg, 8.9 μmol), PPh_3 (3.9 mg, 14.9 μmol) and potassium carbonate (82 mg, 0.59 mmol) in toluene (2.5 mL) were reacted for 16 hr. Work-up as specified gave a mixture of recovered reagents and none of the desired product.

Synthesis method b. Using General Method 13, **45l** (167 mg, 0.47 mmol) and 4-pyridinylboronic acid (117 mg, 0.95 mmol) were reacted with $Pd(OAc)_2$ (3.2 mg, 14 μmol), PPh_3 (6.3 mg, 24 μmol) and potassium carbonate (132 mg, 0.96 mmol) in toluene/ethanol (1:1, 2.5 mL) for 16 hr. The crude mixture was purified by column chromatography on silica gel eluting with 1:1 ethyl acetate/hexane to give **122b** as a pale yellow solid (166 mg, 100%). $R_f = 0.33$ (1:1 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{26}N_2O_2$: 351.2073; found 351.2068. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 [9H, s, ^{t}Bu], 2.33-2.42 [2H, m, H(5)], 2.46-2.54 [2H, m, H(3)], 3.39-3.47 [2H, m, H(2)], 3.50-3.58 [2H, m, H(6)], 6.43 [1H, s, H(A)], 7.26-7.29 [1H, m, H(6')], 7.42-7.53 [5H, m, H(2') + H(4') + H(5') + H(2") + H(6")], 8.64-8.69 [2H, m, H(3") + H(5")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.60 [^{t}Bu], 29.45 [br, C(3)], 36.35 [br, C(5)], 45.01 [br, C(2) + C(6)], 79.78 [^{t}Bu], 121.77 [C(2") + C(6")], 124.13 [C(A)], 125.11 [C(5')], 127.69 [C(2')], 129.12 [C(4')], 129.65 [C(6')], 138.30 [C(3')], 138.48 [C(1')], 139.63 [C(4)], 148.40 [C(1")], 150.41 [C(3") + C(5")], 154.87 [C=O].

***tert*-Butyl 4-(2-(pyridin-4-yl)benzylidene)piperidine-1-carboxylate (122a)**

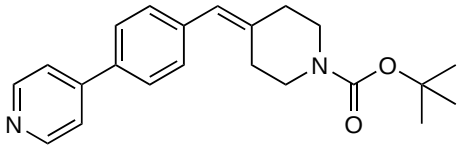


Using General Method 13, **45k** (164 mg, 0.47 mmol), 4-pyridinylboronic acid (80 mg, 0.65 mmol), $Pd(OAc)_2$ (3.1 mg, 14 μmol), PPh_3 (6.1 mg, 23 μmol) and potassium carbonate (129 mg, 0.93 mmol) in toluene/ethanol (1:1, 2.5 mL) were reacted for 16 hr. Work-up as specified

and column chromatography on silica gel eluting with 2:3 ethyl acetate/hexane gave **122a** as a pale yellow oil (101 mg, 62%). R_f = 0.21 (2:3 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{26}N_2O_2$: 351.2073; found 351.2069. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 [9H, s, ^{t}Bu], 2.16-2.26 [4H, m, H(3) + H(5)], 3.19-3.29 [2H, m, H(2)], 3.39-3.46 [2H, m, H(6)], 6.16 [1H, s, H(A)], 7.23-7.41 [6H, m, H(3') + H(4') + H(5') + H(6') + H(2") + H(6")], 8.59-8.65 [2H, m, H(3") + H(5")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.55 [^{t}Bu], 29.43 [br, C(3)], 36.00 [br, C(5)], 44.94 [br, C(2) + C(6)], 79.72 [^{t}Bu], 123.53 [C(A)], 124.61 [C(2") + C(6")], 127.37 [*C(3')], 128.35 [*C(6')], 129.51 [*C(4')], 130.58 [*C(5')], 135.56 [C(2')], 138.56 [C(1')], 139.12 [C(4)], 149.35 [C(1")], 149.58 [C(3") + C(5")], 154.77 [C=O].

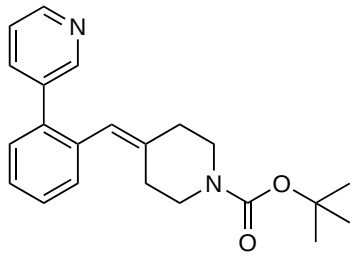
*Interpretation of spectra and 2D NMR correlations could not achieve unambiguous assignment of all NMR signals due to overlapped signals in the ^{1}H NMR spectrum.

tert-Butyl 4-(4-(pyridin-4-yl)benzylidene)piperidine-1-carboxylate (122c)



Using General Method 13, **45m** (160 mg, 0.45 mmol), 4-pyridinylboronic acid (98 mg, 0.80 mmol), $Pd(OAc)_2$ (3.8 mg, 17 μmol), PPh_3 (7.4 mg, 28 μmol) and potassium carbonate (157 mg, 1.14 mmol) in toluene/ethanol (1:1, 2.5 mL) were reacted for 16 hr. Work-up as specified and column chromatography on silica gel eluting with 2:3 ethyl acetate/hexane gave **122c** as a pale colourless oil (159 mg, 100%). R_f = 0.18 (3:7 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{26}N_2O_2 - C(CH_3)_3$: 295.1447; found 295.1446. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.32-2.40 [2H, m, H(5)], 2.46-2.55 [2H, m, H(3)], 3.39-3.47 [2H, m, H(2)], 3.50-3.57 [2H, m, H(6)], 6.40 [1H, s, H(A)], 7.29-7.34 [2H, m, H(2') + H(6')], 7.48-7.53 [2H, m, H(2") + H(6")], 7.58-7.63 [2H, m, H(3') + H(5')], 8.63-8.67 [2H, m, H(3") + H(5")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.61 [^{t}Bu], 29.49 [br, C(5)], 36.45 [br, C(3)], 45.54 [br, C(2) + C(6)], 79.79 [^{t}Bu], 121.50 [C(2") + C(6")], 123.97 [C(A)], 126.90 [C(3') + C(5')], 129.77 [C(2') + C(6')], 136.06 [C(4')], 138.56 [C(1')], 139.84 [C(4)], 148.02 [C(1")], 150.41 [C(3") + C(5")], 154.89 [C=O].

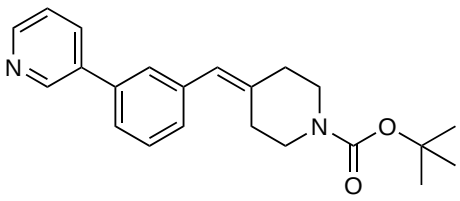
tert-Butyl 4-(2-(pyridin-3-yl)benzylidene)piperidine-1-carboxylate (123a)



Using General Method 13, **36k** (200 mg, 0.57 mmol), 3-pyridinylboronic acid (140 mg, 1.1 mmol), $Pd(OAc)_2$ (2.8 mg, 17 μmol), PPh_3 (7.4 mg, 28 μmol) and potassium carbonate (157 mg, 1.1 mmol) in toluene/ethanol (1:1, 2.5 mL) were reacted for 16 hr. Work-up as specified and column chromatography on silica gel eluting with 1:1 ethyl acetate/hexane gave **123a** as a colourless oil (113 mg, 57%). R_f = 0.47 (1:1 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{26}N_2O_2$: 351.2073; found 351.2066. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 [9H, s, ^{t}Bu], 2.12-2.31 [4H, m, H(3) + H(5)], 3.15-3.32 [2H, m, H(2)], 3.36-3.46 [2H, m, H(6)], 6.16 [1H, s, H(A)], 7.23-7.39 [5H, m, H(3') + H(4') + H(5') + H(6') + H(5")], 7.65-7.70 [1H, m, H(6")], 8.56 [1H, d, $^3J_{4",5"}$ = 4.5 Hz, H(4")], 8.62 [1H, s, H(2")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.55 [^{t}Bu], 29.46 [br, C(3)], 35.98 [br, C(5)], 44.83 [br, C(2) + C(6)], 79.59 [^{t}Bu], 122.97 [C(5")], 123.66 [C(A)], 127.37 [C(4')], 127.92 [*C(3') or C(5')], 129.93 [*C(3') or C(5')], 130.52 [C(6')], 135.91 [C(1')], 136.85 [C(6")], 137.11 [C(2')], 137.60 [C(1")], 139.04 [C(4)], 148.19 [C(4")], 150.45 [C(2")], 154.80 [C=O].

*Interpretation of spectra and 2D NMR correlations could not achieve unambiguous assignment of all NMR signals due to overlapped signals in the ^{1}H NMR spectrum.

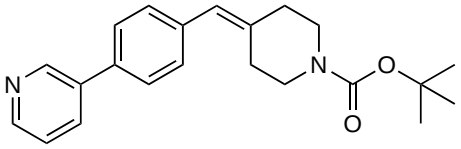
tert-Butyl 4-(3-(pyridin-3-yl)benzylidene)piperidine-1-carboxylate (123b)



Using General Method 13, **36l** (200 mg, 0.57 mmol), 3-pyridinylboronic acid (98 mg, 0.80 mmol), $Pd(OAc)_2$ (3.8 mg, 17 μmol), PPh_3 (7.4 mg, 28 μmol) and potassium carbonate (157 mg, 1.14 mmol) in toluene/ethanol (1:1, 2.5 mL) were reacted for 16 hr. Work-up as specified and column chromatography on silica gel eluting with 1:3 ethyl acetate/hexane gave **123b** as a colourless oil (182 mg, 91%). R_f = 0.14 (1:3 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{26}N_2O_2$: 351.2073; found 351.2068. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.33-2.40 [2H, m, H(5)], 2.47-2.53 [2H, m, H(3)], 3.39-3.46 [2H, m, H(2)],

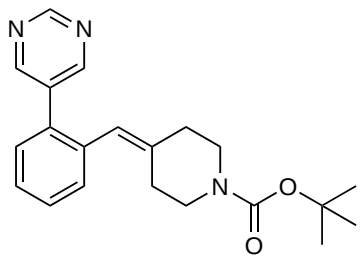
3.50-3.56 [2H, m, H(6)], 6.43 [1H, s, H(A)], 7.21-7.26 [1H, m, H(5')], 7.36 [1H, dd, $^3J_{5'',6''}$ = 7.9 Hz, $^3J_{4'',5''}$ = 4.8 Hz, H(5'')], 7.39 [1H, s, H(2')], 7.41-7.47 [2H, m, H(4') + H(6')], 7.84-7.89 [1H, m, H(6'')], 8.60 [1H, dd, $^3J_{4'',5''}$ = 4.8 Hz, $^4J_{4'',6''}$ = 1.2 Hz, H(4'')], 8.84 [1H, d, $^4J_{2'',6''}$ = 2.0 Hz, H(2'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.60 [^{t}Bu], 29.47 [br, C(3)], 36.36 [br, C(5)], 45.24 [br, C(2) + C(6)], 79.76 [^{t}Bu], 123.67 [C(5'')], 124.25 [C(A)], 125.27 [C(4')], 127.85 [C(2')], 128.73 [C(5')], 129.08 [C(6')], 134.47 [C(6')], 136.70 [C(3'')], 137.97 [C(3')], 138.43 [C(1')], 139.47 [C(4)], 148.49 [C(2'')], 148.68 [C(4'')], 154.88 [C=O].

tert-Butyl 4-(4-(pyridin-3-yl)benzylidene)piperidine-1-carboxylate (123c)



Using General Method 13, **36m** (300 mg, 0.98 mmol), 3-pyridinylboronic acid (180 mg, 1.46 mmol), $Pd(OAc)_2$ (6.6 mg, 29 μmol), PPh_3 (13 mg, 49 μmol) and potassium carbonate (270 mg, 2.0 mmol) in toluene/ethanol (1:1, 2.5 mL) were reacted for 16 hr. Work-up as specified and column chromatography on silica gel eluting with 2:3 ethyl acetate/hexane gave **123c** as a colourless oil (151 mg, 51%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{26}N_2O_2$: 351.2073; found 351.2072. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 [9H, s, ^{t}Bu], 2.33-2.41 [2H, m, H(5)], 2.47-2.55 [2H, m, H(3)], 3.38-3.48 [2H, m, H(2)], 3.49-3.58 [2H, m, H(6)], 6.40 [1H, s, H(A)], 7.28-7.33 [2H, m, H(2') + H(6')], 7.35 [1H, dd, $^3J_{5'',6''}$ = 7.9 Hz, $^3J_{4'',5''}$ = 4.8 Hz, H(5'')], 7.52-7.58 [2H, m, H(3') + H(5')], 7.87 [1H, ddd, $^3J_{5'',6''}$ = 7.9 Hz, $^4J_{2'',6''}$ = 2.2 Hz, $^4J_{4'',6''}$ = 1.6 Hz, H(6'')], 8.58 [1H, dd, $^3J_{4'',5''}$ = 4.8 Hz, $^4J_{4'',6''}$ = 1.6 Hz, H(4'')], 8.86 [1H, d, $^4J_{2'',6''}$ = 2.2 Hz, H(2'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.57 [^{t}Bu], 29.43 [br, C(3)], 36.39 [br, C(5)], 45.22 [br, C(2) + C(6)], 79.71 [^{t}Bu], 123.64 [C(5'')], 124.01 [C(A)], 126.98 [C(3') + C(5')], 129.72 [C(2') + C(6')], 134.19 [C(6'')], 135.80 [C(4')], 136.35 [C(1'')], 137.49 [C(1')], 139.43 [C(4)], 148.29 [C(2'')], 148.50 [C(4'')], 154.85 [C=O].

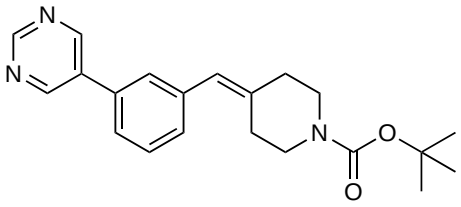
tert-Butyl 4-(2-(pyrimidin-5-yl)benzylidene)piperidine-1-carboxylate (124a)



Using General Method 13, **45k** (200 mg, 0.57 mmol), 5-pyrimidinylboronic acid (85 mg, 0.69 mmol), $Pd(OAc)_2$ (3.8 mg, 17 μmol), PPh_3 (7.4 mg, 28 μmol) and potassium carbonate (157

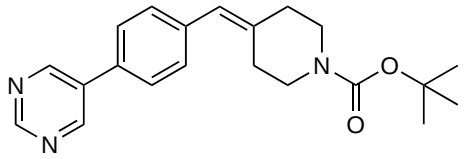
mg, 1.14 mmol) in toluene/ethanol (1:1, 2.5 mL) were reacted for 16 hr. Work-up as specified and column chromatography on silica gel eluting with 2:3 ethyl acetate/hexane gave **124a** as a colourless oil (172 mg, 86%). R_f = 0.26 (2:3 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{25}N_3O_2$: 352.2025; found 352.2028. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 [9H, s, ^{t}Bu], 2.13-2.31 [4H, m, H(3) + H(5)], 3.22-3.36 [2H, m, H(2)], 3.40-3.48 [2H, m, H(6)], 6.17 [1H, s, H(A)], 7.29 [1H, d, $^3J_{5',6'}$ = 7.3 Hz, H(6')], 7.34 [1H, d, $^3J_{3',4'}$ = 7.3 Hz, H(3')], 7.36-7.45 [2H, m, H(4') + H(5')], 8.76 [2H, s, H(2'') + H(6'')], 9.17 [1H, s, H(4'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.53 [^{t}Bu], 29.49 [br, C(3)], 35.95 [br, C(5)], 44.98 [br, C(2) + C(6)], 79.78 [^{t}Bu], 122.92 [C(A)], 127.72 [C(4')], 128.84 [C(5')], 129.74 [C(3')], 130.83 [C(6')], 133.81 [C(2')], 134.98 [C(1'')], 136.06 [C(1')], 140.31 [C(4)], 154.73 [C=O], 156.93 [C(2'') + C(6'')], 157.19 [C(4'')].

tert-Butyl 4-(3-(pyrimidin-5-yl)benzylidene)piperidine-1-carboxylate (124b)



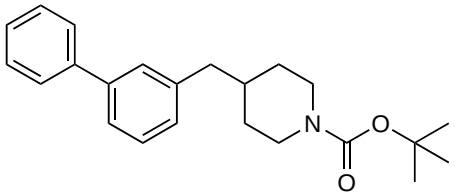
Using General Method 13, **36l** (200 mg, 0.57 mmol), 5-pyrimidinylboronic acid (99 mg, 0.80 mmol), $Pd(OAc)_2$ (3.8 mg, 17 μmol), PPh_3 (7.4 mg, 28 μmol) and potassium carbonate (157 mg, 1.14 mmol) in toluene/ethanol (1:1, 2.5 mL) were reacted for 16 hr. Work-up as specified and column chromatography on silica gel eluting with 1:1 ethyl acetate/hexane gave **124b** as a yellow solid (173 mg, 87%). R_f = 0.41 (1:1 ethyl acetate/hexane). MP: 120-121°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{25}N_3O_2 - C(CH_3)_3$: 296.1399; found 296.1394. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [9H, s, ^{t}Bu], 2.34-2.41 [2H, m, H(5)], 2.46-2.53 [2H, m, H(3)], 3.39-3.46 [2H, m, H(2)], 3.51-3.57 [2H, m, H(6)], 6.43 [1H, s, H(A)], 7.30 [1H, d, $^3J_{5',6'}$ = 7.6 Hz, H(6')], 7.39 [1H, s, H(2')], 7.43 [1H, d, $^3J_{4',5'}$ = 7.6 Hz, H(4')], 7.48 [1H, t, $^3J_{4',5'}$ = $^3J_{5',6'}$ = 7.6 Hz, H(5')], 8.95 [2H, s, H(2'') + H(6'')], 9.21 [1H, s, H(4'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.59 [^{t}Bu], 29.47 [br, C(3)], 36.34 [br, C(5)], 45.15 [br, C(2) + C(6)], 79.81 [^{t}Bu], 123.90 [C(A)], 125.06 [C(4')], 127.64 [C(2')], 129.44 [C(5')], 129.61 [C(6')], 134.42 [C(3') + C(1'')], 138.85 [C(1')], 139.99 [C(4)], 154.85 [C=O], 155.04 [C(2'') + C(6'')], 157.67 [C(4'')].

tert-Butyl 4-(4-(pyrimidin-5-yl)benzylidene)piperidine-1-carboxylate (124c)



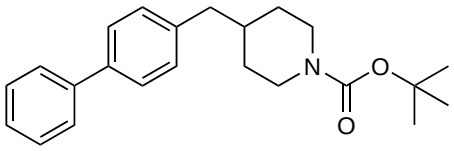
Using General Method 13, **36m** (200 mg, 0.57 mmol), 5-pyrimidinylboronic acid (85 mg, 0.69 mmol), $Pd(OAc)_2$ (3.8 mg, 17 μmol), PPh_3 (7.4 mg, 28 μmol) and potassium carbonate (157 mg, 1.14 mmol) in toluene/ethanol (1:1, 2.5 mL) were reacted for 16 hr. Work-up as specified and column chromatography on silica gel eluting with 1:4 ethyl acetate/hexane gave **124c** as a colourless oil (184 mg, 92%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{25}N_3O_2 - C(CH_3)_3$: 296.1399; found 296.1389. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 [9H, s, ^{t}Bu], 2.31-2.43 [2H, m, H(5)], 2.46-2.56 [2H, m, H(3)], 3.37-3.49 [2H, m, H(2)], 3.50-3.60 [2H, m, H(6)], 6.41 [1H, s, H(A)], 7.32-7.38 [2H, m, H(2') + H(6')], 7.52-7.58 [2H, m, H(3') + H(5')], 8.96 [2H, s, H(2'') + H(6'')], 9.19 [1H, s, H(4'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.55 [^{t}Bu], 29.42 [br, C(3)], 36.38 [br, C(5)], 44.42 [br, C(2)], 45.47 [br, C(6)], 79.72 [^{t}Bu], 123.73 [C(A)], 126.81 [C(3') + C(5')], 130.02 [C(2') + C(6')], 132.16 [C(4')], 134.06 [C(1'')], 138.43 [C(1')], 140.02 [C(4)], 154.78 [C(2'') + C(6'')], 154.80 [C=O], 157.46 [C(4'')].

tert-Butyl 4-((1,1'-biphenyl)-3-ylmethyl)piperidine-1-carboxylate (125a)



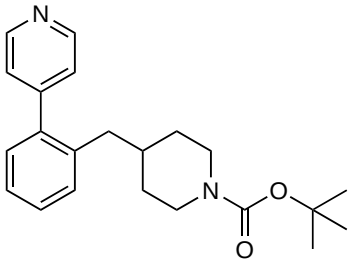
Using General Method 3, **121a** (223 mg, 0.64 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 16 hr. Work-up gave **125a** as a colourless oil (224 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{21}N$: 252.1752; found 252.1749. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05-1.26 [2H, m, $H(3_{ax})$ + $H(5_{ax})$], 1.45 [9H, s, ^{t}Bu], 1.55-1.85 [3H, m, $H(3_{eq})$ + $H(4_{ax})$ + $H(5_{eq})$], 2.49-2.79 [4H, m, $H(2_{ax})$ + $H(6_{ax})$ + H(A)], 3.88-4.28 [2H, m, $H(2_{eq})$ + $H(6_{eq})$], 7.12 [1H, br d‡, $^3J_{5',6'} = 7.5$ Hz, H(6')], 7.30-7.50 [6H, m, H(2') + H(4') + H(5') + H(3'') + H(4'') + H(5'')], 7.54-7.63 [2H, m, H(2'') + H(6'')].

tert-Butyl 4-((1,1'-biphenyl)-4-ylmethyl)piperidine-1-carboxylate (125b)



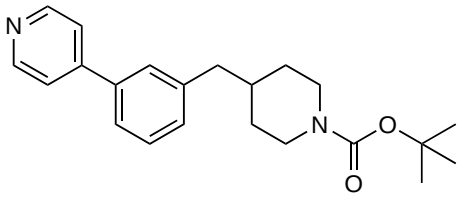
Using General Method 3, **121b** (278 mg, 0.80 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 16 hr. Work-up gave **125b** as a white solid (280 mg, 100%). $R_f = 0.32$ (1:9 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{23}H_{29}NO_2 - C(CH_3)_3$: 296.1651; found 296.1643. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10-1.25 [2H, m, $H(3_{ax}) + H(5_{ax})$], 1.45 [9H, s, ^{t}Bu], 1.61-1.76 [3H, m, $H(3_{eq}) + H(4_{ax}) + H(5_{eq})$], 2.51-2.74 [4H, m, $H(2_{ax}) + H(6_{ax}) + H(A)$], 3.96-4.23 [2H, m, $H(2_{eq}) + H(6_{eq})$], 7.17-7.24 [2H, m, H(2') + H(6')], 7.32 [1H, t, $^3J_{3'',4''} = {}^3J_{4'',5''} = 7.5$ Hz, H(4'')], 7.39-7.46 [2H, m, H(3'') + H(5'')], 7.48-7.54 [2H, m, H(3') + H(5')], 7.55-7.61 [2H, m, H(2'') + H(6'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.62 [^{t}Bu], 32.17 [br, C(3) + C(5)], 38.33 [C(4)], 42.92 [C(A)], 44.33 [br, C(2) + C(6)], 79.38 [^{t}Bu], 127.11 [C(3') + C(5')], 127.11 [C(2'') + C(6'')], 127.19 [C(4'')], 128.86 [C(3'') + C(5'')], 129.67 [C(2') + C(6')], 139.04 [C(4')], 139.50 [C(1')], 141.14 [C(1'')], 155.02 [C=O].

tert-Butyl 4-(2-(pyridin-4-yl)benzyl)piperidine-1-carboxylate (126a)



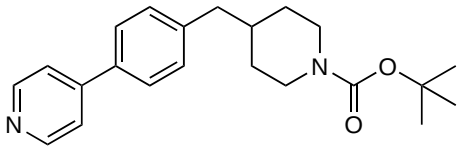
Using General Method 3, **122a** (111 mg, 0.32 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 16 hr. Work-up gave **126a** as a colourless oil (112 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{28}N_2O_2 - C(CH_3)_3$: 297.1603; found 297.1593. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.1$ Hz, $^3J_{(2/6)eq,(3/5)ax} = 3.6$ Hz, $H(3_{ax}) + H(5_{ax})$], 1.36-1.52 [12H, m, ^{t}Bu + $H(3_{eq}) + H(4_{ax}) + H(5_{eq})$], 2.39-2.63 [4H, m, $H(2_{ax}) + H(6_{ax}) + H(A)$], 3.97 [2H, br s‡, $H(2_{eq}) + H(6_{eq})$], 7.16 [1H, br d‡, $^3J_{3',4'} = 7.7$ Hz, H(3')], 7.20-7.25 [2H, m, H(2'') + H(6'')], 7.25-7.31 [2H, m, H(4') + H(6')], 7.34 [1H, td, $^3J_{4',5'} = {}^3J_{5',6'} = 7.7$ Hz, $^4J_{3',5'} = 1.2$ Hz, H(5')], 8.62-8.69 [2H, m, H(3'') + H(5'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.56 [^{t}Bu], 32.98 [br, C(3) + C(5)], 37.92 [C(4)], 39.65 [C(A)], 43.67 [br, C(2) + C(6)], 79.38 [^{t}Bu], 124.57 [C(2'') + C(6'')], 126.35 [C(4')], 128.38 [C(5')], 129.68 [C(3')], 130.36 [C(6')], 137.39 [C(1')], 139.67 [C(2')], 149.77 [C(3'') + C(5'')], 150.10 [C(1'')], 154.86 [C=O].

tert-Butyl 4-(3-(pyridin-4-yl)benzyl)piperidine-1-carboxylate (126b)



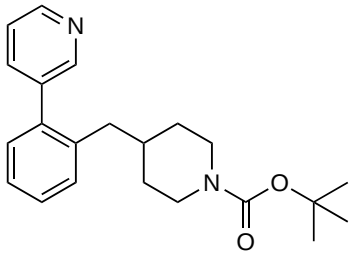
Using General Method 3, **122b** (137 mg, 0.39 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 16 hr. Work-up gave **126b** as a yellow oil (138 mg, 100%). R_f = 0.29 (1:1 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{28}N_2O_2$: 353.2229; found 353.2222. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax}$ = 11.8 Hz, $^3J_{(2/6)eq,(3/5)ax}$ = 2.9 Hz, H(3_{ax}) + H(5_{ax})], 1.45 [9H, s, ^{t}Bu], 1.59-1.78 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.57-2.71 [4H, m, H(2_{ax}) + H(6_{ax}) + H(A)], 3.95-4.26 [2H, m, H(2_{eq}) + H(6_{eq})], 7.22 [1H, d, $^3J_{5',6'}$ = 7.5 Hz, H(6')], 7.38-7.43 [2H, m, H(2') + H(5')], 7.46-7.53 [3H, m, H(4') + H(2") + H(6")], 8.63-8.68 [2H, m, H(3") + H(5")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.61 [^{t}Bu], 32.13 [br, C(3) + C(5)], 38.36 [C(4)], 43.32 [C(A)], 44.09 [br, C(2) + C(6)], 79.44 [^{t}Bu], 121.82 [C(2") + C(6")], 124.86 [C(4')], 127.88 [C(2')], 129.18 [C(5')], 130.00 [C(6')], 138.34 [C(3')], 141.37 [C(1')], 148.52 [C(1")], 150.38 [C(3") + C(5")], 154.98 [C=O].

tert-Butyl 4-(4-(pyridin-4-yl)benzyl)piperidine-1-carboxylate (126c)



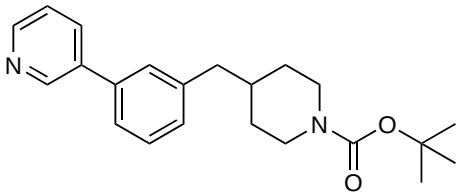
Using General Method 3, **122c** (167 mg, 0.48 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 16 hr. Work-up gave **126c** as a yellow oil (130 mg, 77%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{28}N_2O_2$: 353.2229; found 353.2224. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 [2H, br qd‡, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax}$ = 12.2 Hz, $^3J_{(2/6)eq,(3/5)ax}$ = 3.7 Hz, H(3_{ax}) + H(5_{ax})], 1.45 [9H, s, ^{t}Bu], 1.59-1.77 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.55-2.73 [4H, m, H(2_{ax}) + H(6_{ax}) + H(A)], 3.94-4.27 [2H, m, H(2_{eq}) + H(6_{eq})], 7.22-7.30 [2H, m, H(2') + H(6')], 7.45-7.52 [2H, m, H(2") + H(6")], 7.53-7.60 [2H, m, H(3') + H(5')], 8.62-8.66 [2H, m, H(3") + H(5")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.61 [^{t}Bu], 32.11 [br, C(3) + C(5)], 38.26 [C(4)], 42.95 [C(A)], 44.04 [br, C(2) + C(6)], 79.42 [^{t}Bu], 121.54 [C(2") + C(6")], 126.98 [C(3') + C(5')], 130.02 [C(2') + C(6')], 135.93 [C(4')], 141.63 [C(1')], 148.21 [C(1")], 150.37 [C(3") + C(5")], 154.98 [C=O].

tert-Butyl 4-(2-(pyridin-3-yl)benzyl)piperidine-1-carboxylate (127a)



Using General Method 3, **123a** (110 mg, 0.31 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 16 hr. Work-up gave **127a** as a pale yellow oil (103 mg, 93%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{28}N_2O_2$: 353.2229; found 353.2218. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 [2H, br qd‡, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.1$ Hz, $^3J_{(2/6)eq,(3/5)ax} = 3.3$ Hz, H(3_{ax}) + H(5_{ax})], 1.35-1.51 [12H, m, ^{t}Bu + H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.43-2.58 [4H, m, H(2_{ax}) + H(6_{ax}) + H(A)], 3.96 [2H, br s‡, H(2_{eq}) + H(6_{eq})], 7.19 [1H, br d‡, $^3J_{3',4'} = 7.6$ Hz, H(3')], 7.32-7.38 [2H, m, H(5') + H(5'')], 7.32-7.38 [2H, m, H(4') + H(6')], 7.61 [1H, dt, $^3J_{5'',6''} = 7.8$ Hz, $^4J_{2'',6''} = {}^4J_{4'',6''} = 1.5$ Hz, H(6'')], 8.56 [1H, d, $^4J_{2'',6''} = 1.5$ Hz, H(2'')], 8.61 [1H, dd, $^3J_{4'',5''} = 4.6$ Hz, $^4J_{4'',6''} = 1.5$ Hz, H(4'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.58 [^{t}Bu], 32.01 [br, C(3) + C(5)], 37.93 [C(4)], 39.78 [C(A)], 44.13 [br, C(2) + C(6)], 79.39 [^{t}Bu], 123.15 [C(6')], 126.34 [C(5'')], 128.20 [C(4')], 130.34 [C(5')], 130.45 [C(3')], 136.74 [C(6'')], 137.64 [C(1'')], 138.11 [C(1')], 138.59 [C(2')], 148.37 [C(4'')], 150.16 [C(2'')], 154.89 [C=O].

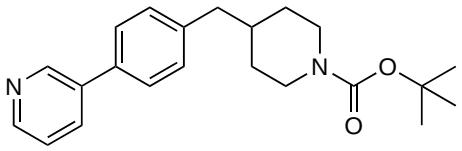
tert-Butyl 4-(3-(pyridin-3-yl)benzyl)piperidine-1-carboxylate (127b)



Using General Method 3, **123b** (182 mg, 0.52 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 16 hr. Work-up gave **127b** as a colourless oil (183 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{28}N_2O_2$: 353.2229; found 353.2226. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 [2H, br qd‡, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.2$ Hz, $^3J_{(2/6)eq,(3/5)ax} = 3.6$ Hz, H(3_{ax}) + H(5_{ax})], 1.45 [9H, s, ^{t}Bu], 1.58-1.78 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.55-2.74 [4H, m, H(2_{ax}) + H(6_{ax}) + H(A)], 4.09 [2H, br s‡, H(2_{eq}) + H(6_{eq})], 7.18 [1H, br d‡, $^3J_{3',4'} = 7.1$ Hz, H(6')], 7.32-7.45 [4H, m, H(2') + H(4') + H(5') + H(5'')], 7.87 [1H, ddd, $^3J_{5'',6''} = 7.9$ Hz, $^4J_{2'',6''} = 2.0$ Hz, $^4J_{4'',6''} = 1.6$ Hz, H(6'')], 8.59 [1H, dd, $^3J_{4'',5''} = 4.8$ Hz, $^4J_{4'',6''} = 1.6$ Hz, H(4'')], 8.84 [1H, d, $^4J_{2'',6''} = 2.0$ Hz, H(2'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.60 [^{t}Bu], 32.13 [br, C(3) + C(5)], 38.32

[C(4)], 43.31 [C(A)], 44.07 [br, C(2) + C(6)], 79.39 [^{t}Bu], 123.62 [C(5'')], 124.98 [C(4')], 128.04 [C(2')], 129.02 [C(6')], 129.12 [C(5')], 134.47 [C(6'')], 136.79 [C(1'')], 138.00 [C(3')], 141.29 [C(1')], 148.50 [C(2'')], 148.59 [C(4'')], 154.97 [C=O].

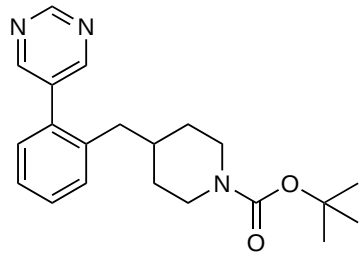
tert-Butyl 4-(4-(pyridin-3-yl)benzyl)piperidine-1-carboxylate (127c)



Using General Method 3, **123c** (135 mg, 0.39 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 16 hr. Work-up gave **127c** as a colourless oil (135 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{28}N_2O_2$: 353.2229; found 353.2225. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 [2H, br qd‡, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.4$ Hz, $^3J_{(2/6)eq,(3/5)ax} = 4.1$ Hz, H(3_{ax}) + H(5_{ax})], 1.45 [9H, s, ^{t}Bu], 1.58-1.77 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.56-2.73 [4H, m, H(2_{ax}) + H(6_{ax}) + H(A)], 4.09 [2H, br s‡, H(2_{eq}) + H(6_{eq})], 7.22-7.28 [2H, m, H(2') + H(6')], 7.35 [1H, ddd, $^3J_{5'',6''} = 7.9$ Hz, $^3J_{4'',5''} = 4.8$ Hz, $^5J_{2'',5''} = 0.6$ Hz, H(5'')], 7.47-7.54 [2H, m, H(3') + H(5')], 7.86 [1H, ddd, $^3J_{5'',6''} = 7.9$ Hz, $^4J_{2'',6''} = 2.0$ Hz, $^4J_{4'',6''} = 1.6$ Hz, H(6'')], 8.57 [1H, dd, $^3J_{4'',5''} = 4.8$ Hz, $^4J_{4'',6''} = 1.6$ Hz, H(4'')], 8.84 [1H, br d‡, $^4J_{2'',6''} = 2.0$ Hz, H(2'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.59 [^{t}Bu], 32.11 [br, C(3) + C(5)], 38.27 [C(4)], 42.89 [C(A)], 44.10 [br, C(2) + C(6)], 79.38 [^{t}Bu], 123.63 [C(5'')], 127.09 [C(3') + C(5')], 129.97 [C(2') + C(6')], 134.25 [C(6'')], 135.63 [C(4')], 136.55 [C(1'')], 140.47 [C(1')], 148.31 [*C(2'')], 148.38 [*C(4'')], 154.97 [C=O].

*Some ^{13}C NMR signals could not be unambiguously assigned due to close proximity of chemical shifts.

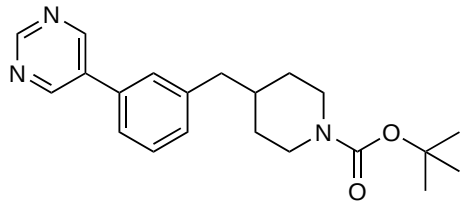
tert-Butyl 4-(2-(pyrimidin-5-yl)benzyl)piperidine-1-carboxylate (128a)



Using General Method 3, **124a** (162 mg, 0.46 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 16 hr. Work-up gave **128a** as a colourless oil (156 mg, 96%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{27}N_3O_2 - C(CH_3)_3$: 298.1556; found 298.1557. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 [2H, br qd‡, $^2J_{(3/5)ax,(3/5)eq} =$

$^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.2$ Hz, $^3J_{(2/6)eq,(3/5)ax} = 2.9$ Hz, H(3_{ax}) + H(5_{ax})], 1.36-1.51 [12H, m, ^{t}Bu + H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.46-2.59 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.99 [2H, br s‡, H(2_{eq}) + H(6_{eq})], 7.19 [1H, d, $^3J_{3',4'} = 7.4$ Hz, H(3')], 7.29-7.36 [2H, m, H(4') + H(6')], 7.40 [1H, br t‡, $^3J_{4',5'} = {}^3J_{5',6'} = 7.4$ Hz, H(5')], 8.71 [2H, s, H(2") + H(6")], 9.23 [1H, s, H(4")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.54 [^{t}Bu], 31.96 [C(3) + C(5)], 38.02 [C(4)], 39.75 [C(A)], 43.90 [br, C(2) + C(6)], 79.44 [^{t}Bu], 126.70 [C(4')], 129.05 [C(5')], 130.43 [C(3')], 130.61 [C(6')], 134.67 [C(2')], 135.54 [C(1")], 138.21 [C(1')], 154.80 [C=O], 156.82 [C(2") + C(6")], 157.45 [C(4")].

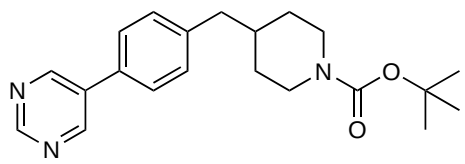
tert-Butyl 4-(3-(pyrimidin-5-yl)benzyl)piperidine-1-carboxylate (128b)



Using General Method 3, **124b** (173 mg, 0.49 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 16 hr. Work-up gave **128b** as a colourless oil (174 mg, 100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.2$ Hz, $^3J_{(2/6)eq,(3/5)ax} = 3.9$ Hz, H(3_{ax}) + H(5_{ax})], 1.45 [9H, s, ^{t}Bu], 1.59-1.79 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.55-2.75 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.97-4.23 [2H, m, H(2_{eq}) + H(6_{eq})], 7.25 [1H, dt, $^3J_{5',6'} = 6.9$ Hz, $^4J_{2',6'} = {}^4J_{4',6'} = 1.7$ Hz, H(6')], 7.35 [1H, br s‡, H(2')], 7.39-7.47 [2H, m, H(4') + H(5')], 8.95 [2H, s, H(2") + H(6")], 9.20 [1H, s, H(4")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.56 [^{t}Bu], 32.07 [br, C(3) + C(5)], 38.26 [C(4)], 43.21 [C(A)], 43.99 [br, C(2) + C(6)], 79.39 [^{t}Bu], 124.79 [C(4')], 127.78 [C(2')], 129.45 [C(5')], 129.89 [C(6')], 134.42 [*C(3') or C(1")], 134.45 [*C(3') or C(1")], 141.72 [C(1')], 154.90 [C=O], 155.00 [C(2") + C(6")], 157.56 [C(4")].

*Some ^{13}C NMR signals could not be unambiguously assigned due to close proximity of chemical shifts.

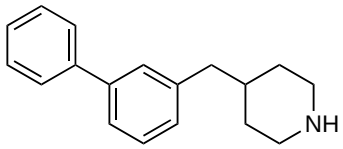
tert-Butyl 4-(4-(pyrimidin-5-yl)benzyl)piperidine-1-carboxylate (128c)



Using General Method 3, **124c** (160 mg, 0.46 mmol) was reacted with Pd-C catalyst in methanol (30 mL) under a hydrogen atmosphere for 16 hr. Work-up gave **128c** as a colourless oil (161 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{27}N_3O_2 - C(CH_3)_3$: 298.1556;

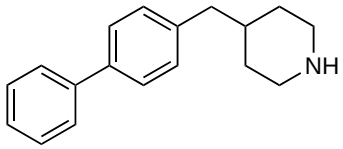
found 298.1559. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.11-1.25 [2H, m, H(3_{ax}) + H(5_{ax})], 1.46 [9H, s, ^{t}Bu], 1.59-1.79 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.58-2.74 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.91-4.23 [2H, m, H(2_{eq}) + H(6_{eq})], 7.27-7.33 [2H, m, H(2') + H(6')], 7.48-7.54 [2H, m, H(3') + H(5')], 8.94 [2H, s, H(2'') + H(6'')], 9.19 [1H, s, H(4'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.56 [^{t}Bu], 32.06 [br, C(3) + C(5)], 38.21 [C(4)], 42.87 [C(A)], 44.12 [br, C(2) + C(6)], 79.37 [^{t}Bu], 126.92 [C(3') + C(5')], 130.29 [C(2') + C(6')], 132.04 [C(4')], 134.22 [C(1'')], 141.51 [C(1')], 154.81 [C(2'') + C(6'')], 154.91 [C=O], 157.40 [C(4'')].

4-((1,1'-Biphenyl)-3-ylmethyl)piperidine (117a)



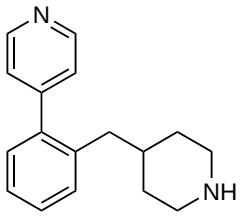
Using General Method 4, **125a** (211 mg, 0.60 mmol) and trifluoroacetic acid (2 mL) were reacted in dichloromethane (10 mL) to give **117a** as a yellow oil (151 mg, 100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27-1.40 [2H, m, H(3_{ax}) + H(5_{ax})], 1.65-1.83 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.54-2.72 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.17 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq}$ = 12.2 Hz, H(2_{eq}) + H(6_{eq})], 4.89 [1H, br s, NH], 7.12 [1H, br d‡, $^{3}J_{5',6'}$ = 7.6 Hz, H(6')], 7.30-7.49 [6H, m, H(2') + H(4') + H(5') + H(3'') + H(4'') + H(5'')], 7.55-7.63 [2H, m, H(2'') + H(6'')].

4-((1,1'-Biphenyl)-4-ylmethyl)piperidine (117b)



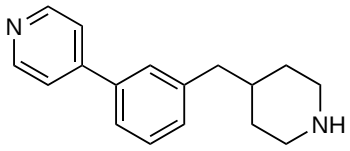
Using General Method 4, **125b** (134 mg, 0.38 mmol) and trifluoroacetic acid (1 mL) were reacted in dichloromethane (4 mL) to give **117b** as a white solid (95 mg, 99%). HRMS (ESI+) $[M+H]^{+}$ calcd. for $C_{18}H_{21}N$: 252.1752; found 252.1751. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 [2H, qd, $^{2}J_{(3/5)ax,(3/5)eq}$ = $^{3}J_{(2/6)ax,(3/5)ax}$ = $^{3}J_{(3/5)ax,4ax}$ = 12.2 Hz, $^{3}J_{(2/6)eq,(3/5)ax}$ = 2.6 Hz, H(3_{ax}) + H(5_{ax})], 1.65-1.80 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.52-2.70 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.18 [2H, br d‡, $^{2}J_{(2/6)ax,(2/6)eq}$ = 12.1 Hz, H(2_{eq}) + H(6_{eq})], 5.12 [1H, br s, NH], 7.17-7.24 [2H, m, H(2') + H(6')], 7.32 [1H, tt, $^{3}J_{3'',4''}$ = $^{3}J_{4'',5''}$ = 7.4 Hz, $^{4}J_{2'',4''}$ = $^{4}J_{4'',6''}$ = 1.1 Hz, H(4'')], 7.39-7.45 [2H, m, H(3'') + H(5'')], 7.48-7.54 [2H, m, H(3') + H(5')], 7.55-7.60 [2H, m, H(2'') + H(6'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.82 [C(3) + C(5)], 37.74 [C(4)], 43.06 [C(A)], 45.86 [C(2) + C(6)], 127.11 [C(2'') + C(6'')], 127.15 [C(3') + C(5')], 127.21 [C(4'')], 128.87 [C(3'') + C(5'')], 129.66 [C(2') + C(6')], 139.14 [C(4')], 139.20 [C(1')], 141.13 [C(1'')].

4-(2-(Piperidin-4-ylmethyl)phenyl)pyridine (118a)



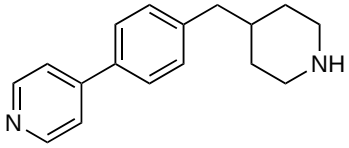
Using General Method 4, **126a** (112 mg, 0.32 mmol) and trifluoroacetic acid (1 mL) were reacted in dichloromethane (4 mL) to give **118a** as a yellow oil (80 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{20}N_2$: 253.1705; found 253.1700. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14-1.30 [2H, m, H(3_{ax}) + H(5_{ax})], 1.37-1.62 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.48-2.65 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.13 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq}$ = 12.4 Hz, H(2_{eq}) + H(6_{eq})], 4.68 [1H, br s, NH], 7.17 [1H, br d‡, $^3J_{3',4'}$ = 7.5 Hz, H(3')], 7.20-7.38 [5H, m, H(4') + H(5') + H(6') + H(2'') + H(6'')], 8.59-8.70 [2H, m, H(3'') + H(5'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.46 [C(3) + C(5)], 36.53 [C(4)], 39.62 [C(A)], 44.99 [C(2) + C(6)], 124.44 [C(2'') + C(6'')], 126.63 [C(4')], 128.48 [C(5')], 129.83 [C(3')], 130.46 [C(6')], 136.66 [C(1')], 139.62 [C(2')], 149.84 [C(3'') + C(5'')], 149.94 [C(1'')].

4-(3-(Piperidin-4-ylmethyl)phenyl)pyridine (118b)



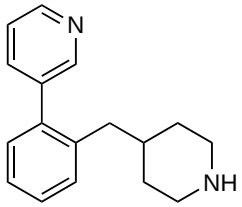
Using General Method 4, **126b** (127 mg, 0.36 mmol) and trifluoroacetic acid (1 mL) were reacted in dichloromethane (4 mL) to give **118b** as a yellow oil (57 mg, 63%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{20}N_2$: 253.1705; found 253.1701. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51-1.64 [2H, m, H(3_{ax}) + H(5_{ax})], 1.75-1.88 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.67 [2H, d, $^3J_{4'ax,A}$ = 6.7 Hz, H(A)], 2.79 [2H, td, $^2J_{(2/6)ax,(2/6)eq}$ = $^3J_{(2/6)ax,(3/5)ax}$ = 12.8 Hz, $^3J_{(2/6)ax,(3/5)eq}$ = 1.9 Hz, H(2_{ax}) + H(6_{ax})], 3.35 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq}$ = 12.8 Hz, H(2_{eq}) + H(6_{eq})], 7.21 [1H, br d‡, $^3J_{5',6'}$ = 7.5 Hz, H(6')], 7.37-7.45 [2H, m, H(2') + H(5')], 7.46-7.77 [4H, m, NH + H(4') + H(2'') + H(6'')], 8.62-8.69 [2H, m, H(3'') + H(5'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.69 [C(3) + C(5)], 39.07 [C(4)], 45.17 [C(A)], 46.87 [C(2) + C(6)], 124.30 [C(2'') + C(6'')], 127.78 [C(4')], 130.27 [C(2')], 131.95 [C(5')], 132.37 [C(6')], 141.12 [C(3')], 142.72 [C(1')], 150.80 [C(1'')], 152.92 [C(3'') + C(5'')].

4-(4-(Piperidin-4-ylmethyl)phenyl)pyridine (118c)



Using General Method 4, **126c** (124 mg, 0.35 mmol) and trifluoroacetic acid (1 mL) were reacted in dichloromethane (4 mL) to give **118c** as a pale yellow solid (85 mg, 96%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{20}N_2$: 253.1705; found 253.1704. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [2H, br qd‡, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.8$ Hz, $^3J_{(2/6)eq,(3/5)ax} = 3.3$ Hz, H(3_{ax}) + H(5_{ax})], 1.71-1.83 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.64 [2H, d, $^3J_{4ax,A} = 6.7$ Hz, H(A)], 2.74 [2H, td, $^2J_{(2/6)ax,(2/6)eq} = {}^3J_{(2/6)ax,(3/5)ax} = 12.8$ Hz, $^3J_{(2/6)ax,(3/5)eq} = 2.7$ Hz, H(2_{ax}) + H(6_{ax})], 3.29 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq} = 12.8$ Hz, H(2_{eq}) + H(6_{eq})], 5.58 [1H, br s, NH], 7.22-7.29 [2H, m, H(2') + H(6')], 7.46-7.51 [2H, m, H(2'') + H(6'')], 7.53-7.61 [2H, m, H(3') + H(5')], 8.60-8.67 [2H, m, H(3'') + H(5'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.31 [C(3) + C(5)], 37.00 [C(4)], 42.64 [C(A)], 44.99 [C(2) + C(6)], 121.55 [C(2'') + C(6'')], 127.11 [C(3') + C(5')], 129.97 [C(2') + C(6')], 136.20 [C(1')], 140.81 [C(4)], 148.12 [C(1'')], 150.36 [C(3'') + C(5'')].

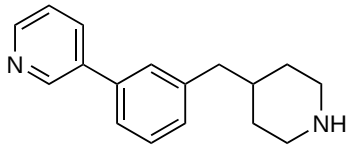
3-(2-(Piperidin-4-ylmethyl)phenyl)pyridine (119a)



Using General Method 4, **127a** (103 mg, 0.29 mmol) and trifluoroacetic acid (1 mL) were reacted in dichloromethane (4 mL) to give **119a** as a yellow oil (73 mg, 99%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{20}N_2$: 253.1705; found 253.1702. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.4$ Hz, $^3J_{(2/6)eq,(3/5)ax} = 3.7$ Hz, H(3_{ax}) + H(5_{ax})], 1.47 [1H, ttt, $^3J_{(3/5)ax,4ax} = 12.4$ Hz, $^3J_{4ax,A} = 7.5$ Hz, $^3J_{(3/5)eq,4ax} = 3.7$ Hz, H(4_{ax})], 1.56 [1H, br d‡, $^2J_{(3/5)ax,(3/5)eq} = 12.4$ Hz, H(3_{eq}) + H(5_{eq})], 2.55-2.64 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.16 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq} = 12.4$ Hz, H(2_{eq}) + H(6_{eq})], 4.20 [1H, br s, NH], 7.20 [1H, dd, $^3J_{3',4'} = 7.5$ Hz, $^4J_{3',5'} = 1.4$ Hz, H(3')], 7.25 [1H, dd, $^3J_{5',6'} = 7.5$ Hz, $^4J_{4',6'} = 1.4$ Hz, H(6')], 7.30 [1H, td, $^3J_{3',4'} = {}^3J_{4',5'} = 7.5$ Hz, $^4J_{4',6'} = 1.4$ Hz, H(4')], 7.32-7.39 [2H, m, H(5') + H(5'')], 7.61 [1H, dt, $^3J_{5'',6''} = 7.7$ Hz, $^4J_{2'',6''} = {}^4J_{4'',6''} = 1.8$ Hz, H(6'')], 8.54 [1H, d, $^4J_{2'',6''} = 1.8$ Hz, H(2'')], 8.60 [1H, dd, $^3J_{4'',5''} = 4.8$ Hz, $^4J_{4'',6''} = 1.8$ Hz, H(4'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 29.83 [C(3) + C(5)], 36.27 [C(4)], 39.51 [C(A)], 44.65 [C(2) + C(6)], 123.26 [C(5'')], 126.69 [C(4')], 128.34 [C(5')],

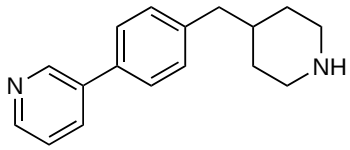
130.39 [C(6')], 130.58 [C(3')], 136.66 [C(6")], 137.18 [C(1')], 137.39 [C(1")], 138.53 [C(2')], 148.48 [C(4")], 149.94 [C(2")].

3-(3-(Piperidin-4-ylmethyl)phenyl)pyridine (119b)



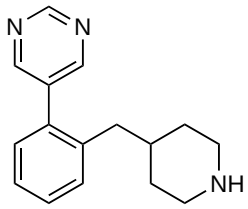
Using General Method 4, **127b** (159 mg, 0.45 mmol) and trifluoroacetic acid (2 mL) were reacted in dichloromethane (8 mL) to give **119b** as a yellow oil (114 mg, 100%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{20}N_2$: 253.1705; found 253.1700. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50-1.63 [2H, m, H(3_{ax}) + H(5_{ax})], 1.76-1.89 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.67 [2H, d, $^3J_{4ax,A}$ = 6.8 Hz, H(A)], 2.79 [2H, td, $^2J_{(2/6)ax,(2/6)eq}$ = $^3J_{(2/6)ax,(3/5)ax}$ = 12.6 Hz, $^3J_{(2/6)ax,(3/5)eq}$ = 2.4 Hz, H(2_{ax}) + H(6_{ax})], 3.34 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq}$ = 12.6 Hz, H(2_{eq}) + H(6_{eq})], 7.07 [1H, br s, NH], 7.18 [1H, br d‡, $^3J_{5',6'}$ = 7.3 Hz, H(6')], 7.32-7.47 [4H, m, H(2') + H(4') + H(5') + H(5")], 7.86 [1H, ddd, $^3J_{5",6"}$ = 7.9 Hz, $^4J_{2",6"}$ = 2.0 Hz, $^4J_{4",6"}$ = 1.6 Hz, H(6")], 8.59 [1H, dd, $^3J_{4",5"}$ = 4.8 Hz, $^4J_{4",6"}$ = 1.6 Hz, H(4")], 8.83 [1H, d, $^4J_{2",6"}$ = 2.0 Hz, H(2")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 29.37 [C(3) + C(5)], 36.63 [C(4)], 42.72 [C(A)], 44.46 [C(2) + C(6)], 123.68 [C(5")], 125.36 [C(4')], 127.93 [C(2')], 128.93 [C(6')], 129.36 [C(5')], 134.50 [C(6")], 136.61 [C(1")], 138.25 [C(3')], 140.21 [C(1')], 148.43 [C(2")], 148.67 [C(4")].

3-(4-(Piperidin-4-ylmethyl)phenyl)pyridine (119c)



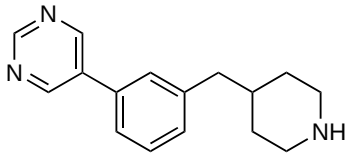
Using General Method 4, **127c** (127 mg, 0.36 mmol) and trifluoroacetic acid (1.5 mL) were reacted in dichloromethane (6 mL) to give **119c** as a yellow oil (89 mg, 98%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34-1.46 [2H, m, H(3_{ax}) + H(5_{ax})], 1.68-1.80 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.56-2.74 [4H, m, H(A) + H(2_{ax}) + H(6_{ax})], 3.22 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq}$ = 12.3 Hz, H(2_{eq}) + H(6_{eq})], 4.03 [1H, br s, NH], 7.21-7.28 [2H, m, H(2') + H(6')], 7.35 [1H, ddd, $^3J_{5",6"}$ = 7.9 Hz, $^3J_{4",5"}$ = 4.8 Hz, $^5J_{2",5"}$ = 0.6 Hz, H(5")], 7.47-7.54 [2H, m, H(3') + H(5')], 7.86 [1H, ddd, $^3J_{5",6"}$ = 7.9 Hz, $^4J_{2",6"}$ = 2.1 Hz, $^4J_{4",6"}$ = 1.7 Hz, H(6")], 8.57 [1H, dd, $^3J_{4",5"}$ = 4.8 Hz, $^4J_{4",6"}$ = 1.7 Hz, H(4")], 8.84 [1H, dd, $^4J_{2",6"}$ = 2.1 Hz, $^5J_{2",5"}$ = 0.6 Hz, H(2")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.09 [C(3) + C(5)], 37.42 [C(4)], 42.85 [C(A)], 45.46 [C(2) + C(6)], 123.67 [C(5")], 127.23 [C(3') + C(5')], 129.97 [C(6")], 134.29 [C(2') + C(6')], 135.88 [C(1")], 136.52 [C(4')], 139.96 [C(1')], 148.38 [C(2")], 148.50 [C(4")].

5-(2-(Piperidin-4-ylmethyl)phenyl)pyrimidine (120a)



Using General Method 4, **128a** (156 mg, 0.44 mmol) and trifluoroacetic acid (1.5 mL) were reacted in dichloromethane (6 mL) to give **120a** as a yellow oil (85 mg, 76%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{19}N_3$: 254.1657; found 254.1653. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 13.0$ Hz, $^3J_{(2/6)eq,(3/5)ax} = 4.0$ Hz, $H(3_{ax}) + H(5_{ax})$], 1.39-1.58 [3H, m, $H(3_{eq}) + H(4_{ax}) + H(5_{eq})$], 2.47-2.61 [4H, m, H(A) + $H(2_{ax}) + H(6_{ax})$], 3.09 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq} = 12.6$ Hz, $H(2_{eq}) + H(6_{eq})$], 5.20 [1H, br s, NH], 7.19 [1H, dd, $^3J_{3',4'} = 7.5$ Hz, $^4J_{3',5'} = 1.4$ Hz, H(3')], 7.28-7.36 [2H, m, H(4') + H(6')], 7.40 [1H, td, $^3J_{4',5'} = {}^3J_{5',6'} = 7.5$ Hz, $^4J_{3',5'} = 1.4$ Hz, H(5')], 8.70 [2H, s, H(2'') + H(6'')], 9.22 [1H, s, H(4'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.25 [C(3) + C(5)], 37.17 [C(4)], 39.88 [C(A)], 45.43 [C(2) + C(6)], 126.84 [C(4)], 129.08 [C(5)], 130.50 [C(3)], 130.68 [C(6)], 134.69 [C(2')], 135.44 [C(1'')], 137.80 [C(1')], 156.77 [C(2'') + C(6'')], 157.50 [C(4'')].

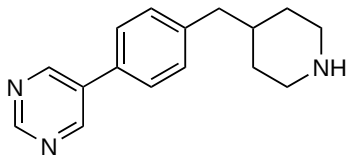
5-(3-(Piperidin-4-ylmethyl)phenyl)pyrimidine (120b)



Using General Method 4, **128b** (146 mg, 0.41 mmol) and trifluoroacetic acid (1.5 mL) were reacted in dichloromethane (6 mL) to give **120b** as a yellow oil (68 mg, 65%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{19}N_3$: 254.1657; found 254.1654. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.7$ Hz, $^3J_{(2/6)eq,(3/5)ax} = 3.2$ Hz, $H(3_{ax}) + H(5_{ax})$], 1.68-1.85 [3H, m, $H(3_{eq}) + H(4_{ax}) + H(5_{eq})$], 2.59-2.75 [4H, m, H(A) + $H(2_{ax}) + H(6_{ax})$], 3.21 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq} = 12.7$ Hz, $H(2_{eq}) + H(6_{eq})$], 4.35 [1H, br s, NH], 7.25 [1H, br d‡, $^3J_{5',6'} = 6.8$ Hz, H(6')], 7.34 [1H, br s‡, H(2')], 7.39-7.47 [2H, m, H(4') + H(5')], 8.94 [2H, s, H(2'') + H(6'')], 9.20 [1H, s, H(4'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.43 [C(3) + C(5)], 37.57 [C(4)], 43.29 [C(A)], 45.61 [C(2) + C(6)], 124.96 [C(4')], 127.80 [C(2')], 129.56 [C(5')], 129.93 [C(6')], 134.46 [*C(3') or C(1'')], 134.54 [*C(3') or C(1'')], 141.38 [C(1')], 155.05 [C(2'') + C(6'')], 157.62 [C(4'')].

*Some ^{13}C NMR signals could not be unambiguously assigned due to close proximity of chemical shifts.

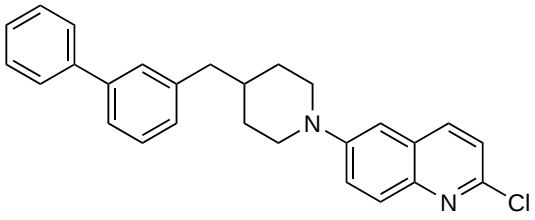
5-(4-(Piperidin-4-ylmethyl)phenyl)pyrimidine (120c)



Using General Method 4, **128c** (135 mg, 0.38 mmol) and trifluoroacetic acid (1.5 mL) were reacted in dichloromethane (6 mL) to give **120c** as a yellow oil (79 mg, 82%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{19}N_3$: 254.1657; found 254.1658. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 [2H, qd, $^2J_{(3/5)ax,(3/5)eq} = {}^3J_{(2/6)ax,(3/5)ax} = {}^3J_{(3/5)ax,4ax} = 12.8$ Hz, $^3J_{(2/6)eq,(3/5)ax} = 2.8$ Hz, H(3_{ax}) + H(5_{ax})], 1.72-1.84 [3H, m, H(3_{eq}) + H(4_{ax}) + H(5_{eq})], 2.65 [2H, d, $^3J_{4ax,A} = 6.7$ Hz, H(A)], 2.73 [2H, td, $^2J_{(2/6)ax,(2/6)eq} = {}^3J_{(2/6)ax,(3/5)ax} = 12.8$ Hz, $^3J_{(2/6)ax,(3/5)eq} = 2.0$ Hz, H(2_{ax}) + H(6_{ax})], 3.28 [2H, br d‡, $^2J_{(2/6)ax,(2/6)eq} = 12.8$ Hz, H(2_{eq}) + H(6_{eq})], 6.32 [1H, br s, NH], 7.27-7.33 [2H, m, H(2') + H(6')], 7.47-7.58 [2H, m, H(3') + H(5')], 8.94 [2H, s, H(2'') + H(6'')], 9.19 [1H, s, H(4'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.49 [C(3) + C(5)], 37.10 [C(4)], 42.68 [C(A)], 45.10 [C(2) + C(6)], 127.11 [C(3') + C(5')], 130.29 [C(2') + C(6')], 132.37 [C(4')], 134.19 [C(1'')], 140.81 [C(1')], 154.88 [C(2'') + C(6'')], 157.51 [C(4'')].

6.3.2 Synthesis of 2-aminoquinoline derivatives with 6-position biaryl-extended substituents

6-(4-((1,1'-Biphenyl)-3-ylmethyl)piperidin-1-yl)-2-chloroquinoline (129a)

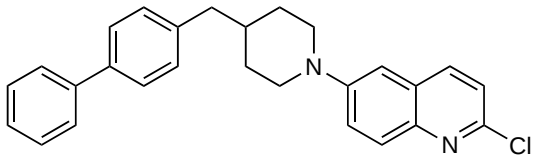


Using General Method 10, **117a** (176 mg, 0.70 mmol) and **24** (202 mg, 0.83 mmol) were reacted with $Pd(OAc)_2$ (0.8 mg, 3.6 μmol), CataCXium® A ligand (2.5 mg, 7.0 μmol) and sodium *tert*-butoxide (87 mg, 0.91 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **129a** as a yellow oil (121 mg, 42%). $R_f = 0.26$ (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{27}H_{25}{}^{35}ClN_2/C_{27}H_{25}{}^{37}ClN_2$: 413.1785/415.1755; found 413.1778/415.1761. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.0$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 3.6$ Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.73-1.91 [3H, m, H($3'_{eq}$) + H($4'_{ax}$) + H($5'_{eq}$)], 2.67 [2H, d, $^3J_{4'ax,A} = 7.0$ Hz, H(A)], 2.77 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = 12.0$ Hz, H($2'_{ax}$) + H($6'_{ax}$)], 3.81 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.0$ Hz, H($2'_{eq}$) + H($6'_{eq}$)], 6.98

[1H, d, $^4J_{5,7}$ = 1.8 Hz, H(5)], 7.16 [1H, d, $^3J_{5'',6''}$ = 7.2 Hz, H(6'')], 7.25 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(3)], 7.32-7.51 [7H, m, H(7) + H(2'') + H(4'') + H(5'') + H(3''') + H(4''') + H(5''')], 7.57-7.64 [2H, m, H(2''') + H(6''')], 7.85 [1H, d, $^3J_{7,8}$ = 9.3 Hz, H(8)], 7.89 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.99 [C(3') + C(5')], 38.05 [C(4')], 43.33 [C(A)], 49.80 [C(2') + C(6')], 108.93 [C(5)], 122.41 [C(3)], 123.76 [C(7)], 125.03 [*C(4'')], 127.31 [C(2''') + C(6''')], 127.41 [C(4''')], 128.14 [*C(6'')], 128.22 [*C(5'')], 128.29 [C(4a)], 128.84 [*C(2'')], 128.89 [C(3''') + C(5''')], 129.15 [C(8)], 137.51 [C(4)], 140.87 [*C(1'')], 141.38 [*C(1''')], 141.39 [*C(3'')], 143.03 [C(8a)], 147.32 [C(2)], 150.12 [C(6)].

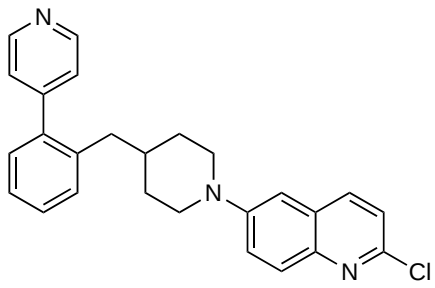
*Interpretation of spectra and 2D NMR correlations could not achieve unambiguous assignment of all NMR signals due to overlapped signals in the ^{1}H NMR spectrum.

6-(4-((1,1'-Biphenyl)-4-ylmethyl)piperidin-1-yl)-2-chloroquinoline (129b)



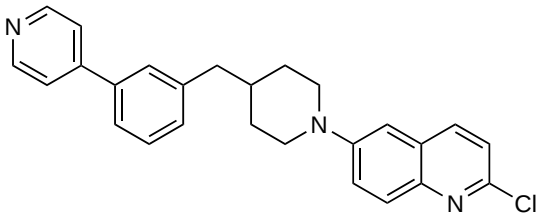
Using General Method 10, **117b** (130 mg, 0.52 mmol) and **24** (150 mg, 0.62 mmol) were reacted with $Pd(OAc)_2$ (0.6 mg, 2.7 μmol), CataCXium® A ligand (1.9 mg, 5.3 μmol) and sodium *tert*-butoxide (95 mg, 0.68 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **129b** as a yellow oil (118 mg, 55%). R_f = 0.22 (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{27}H_{25}{}^{35}ClN_2$/$C_{27}H_{25}{}^{37}ClN_2$: 413.1785/415.1755; found 413.1776/415.1757. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq}$ = $^3J_{(2'/6')ax,(3'/5')ax}$ = $^3J_{(3'/5')ax,4'ax}$ = 11.8 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 2.8 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.72-1.89 [3H, m, H($3'_{eq}$) + H($4'_{ax}$) + H($5'_{eq}$)], 2.63 [2H, d, $^3J_{4'ax,A}$ = 6.9 Hz, H(A)], 2.77 [2H, br t‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = $^3J_{(2'/6')ax,(3'/5')ax}$ = 11.8 Hz, H($2'_{ax}$) + H($6'_{ax}$)], 3.80 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 11.8 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 6.97 [1H, d, $^4J_{5,7}$ = 1.8 Hz, H(5)], 7.21-7.27 [3H, m, H(3) + H(2'') + H(6'')], 7.33 [1H, t, $^3J_{3''',4'''}$ = $^3J_{4''',5'''}$ = 7.2 Hz, H(4''')], 7.39-7.45 [2H, m, H(3''') + H(5''')], 7.48 [1H, dd, $^3J_{7,8}$ = 9.3 Hz, $^4J_{5,7}$ = 1.8 Hz, H(7)], 7.51-7.56 [2H, m, H(3'') + H(5'')], 7.56-7.62 [2H, m, H(2''') + H(6''')], 7.85 [1H, d, $^3J_{7,8}$ = 9.3 Hz, H(8)], 7.88 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.97 [C(3') + C(5')], 37.96 [C(4')], 42.83 [C(A)], 49.77 [C(2') + C(6')], 108.91 [C(5)], 122.38 [C(3)], 123.74 [C(7)], 127.08 [C(2''') + C(6''')], 127.11 [C(3'') + C(5'')], 127.21 [C(4''')], 128.27 [C(4a)], 128.87 [C(3''') + C(5''')], 129.11 [C(8)], 129.67 [C(2'') + C(6'')], 137.49 [C(4)], 139.06 [C(4'')], 139.48 [C(1'')], 141.08 [C(1''')], 143.01 [C(8a)], 147.29 [C(2)], 150.11 [C(6)].

2-Chloro-6-(4-(2-(pyridin-4-yl)benzyl)piperidin-1-yl)quinoline (130a)



Using General Method 10, **118a** (84 mg, 0.33 mmol) and **24** (97 mg, 0.40 mmol) were reacted with $Pd(OAc)_2$ (0.4 mg, 1.8 μmol), CataCXium® A ligand (1.2 mg, 3.3 μmol) and sodium *tert*-butoxide (42 mg, 0.44 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **130a** as a yellow oil (92 mg, 67%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{26}H_{24}{}^{35}ClN_3/C_{26}H_{24}{}^{37}ClN_3$: 414.1737/416.1708; found 414.1727/416.1711. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.0$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 3.3$ Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.45-1.64 [3H, m, H(3'$_{eq}$) + H(4'$_{ax}$) + H(5'$_{eq}$)], 2.55-2.71 [4H, m, H(A) + H(2'$_{ax}$) + H(6'$_{ax}$)], 3.69 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.0$ Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 6.92 [1H, d, $^4J_{5,7} = 2.5$ Hz, H(5)], 7.19 [1H, br d‡, $^3J_{3'',4''} = 7.1$ Hz, H(3'')], 7.22-7.40 [6H, m, H(3) + H(4'') + H(5'') + H(6'') + H(2''') + H(6''')], 7.42 [1H, dd, $^3J_{7,8} = 9.3$ Hz, $^4J_{5,7} = 2.5$ Hz, H(7)], 7.82 [1H, d, $^3J_{7,8} = 9.3$ Hz, H(8)], 7.87 [1H, d, $^3J_{3,4} = 8.6$ Hz, H(4)], 8.62-8.70 [2H, m, H(3''') + H(5''')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.91 [C(3') + C(5')], 37.55 [C(4')], 39.69 [C(A)], 49.76 [C(2') + C(6')], 109.03 [C(5)], 122.43 [C(3)], 123.78 [C(7)], 124.60 [C(2''') + C(6''')], 126.45 [C(4'')], 128.24 [C(4a)], 128.44 [C(5'')], 129.15 [C(8)], 129.77 [C(3'')], 130.46 [C(6'')], 137.44 [C(1'')], 137.50 [C(4)], 139.71 [C(2'')], 143.09 [C(8a)], 147.41 [C(2)], 149.83 [C(3''') + C(5''')], 150.06 [C(6)], 150.15 [C(1''')].

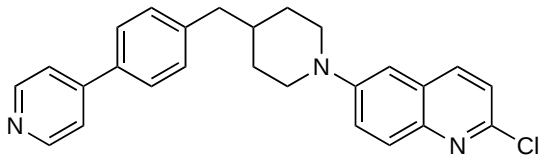
2-Chloro-6-(4-(3-(pyridin-4-yl)benzyl)piperidin-1-yl)quinoline (130b)



Using General Method 10, **118b** (75 mg, 0.30 mmol) and **24** (86 mg, 0.35 mmol) were reacted with $Pd(OAc)_2$ (0.3 mg, 1.3 μmol), CataCXium® A ligand (1.1 mg, 3.1 μmol) and sodium *tert*-butoxide (37 mg, 0.39 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **130b** as a yellow oil (74 mg, 60%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{26}H_{24}{}^{35}ClN_3/C_{26}H_{24}{}^{37}ClN_3$:

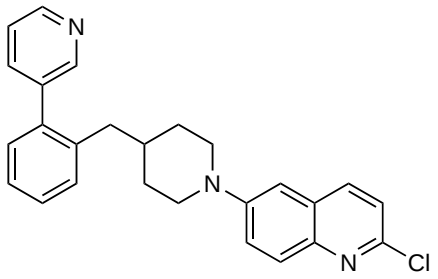
414.1737/416.1708; found 414.1730/416.1714. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [2H, qd, $^{2}J_{(3'/5')ax,(3'/5')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax} = {}^{3}J_{(3'/5')ax,4'ax}$ = 12.0 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.2 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.74-1.89 [3H, m, H(3'$_{eq}$) + H(4'$_{ax}$) + H(5'$_{eq}$)], 2.69 [2H, d, $^{3}J_{4'ax,A}$ = 6.7 Hz, H(A)], 2.78 [2H, t, $^{2}J_{(2'/6')ax,(2'/6')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax}$ = 12.0 Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 3.81 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.0 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 6.98 [1H, d, $^{4}J_{5,7}$ = 2.0 Hz, H(5)], 7.22-7.29 [2H, m, H(3) + H(6'')], 7.39-7.54 [6H, m, H(7) + H(2'') + H(4'') + H(5'') + H(2''') + H(6''')], 7.85 [1H, d, $^{3}J_{7,8}$ = 9.3 Hz, H(8)], 7.88 [1H, d, $^{3}J_{3,4}$ = 8.6 Hz, H(4)], 8.64-8.69 [2H, m, H(3''') + H(5''')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.94 [C(3') + C(5')], 38.01 [C(4')], 43.22 [C(A)], 49.75 [C(2') + C(6')], 108.96 [C(5)], 121.79 [C(2''') + C(6''')], 122.41 [C(3)], 123.70 [C(7)], 124.89 [C(4'')], 127.86 [C(2'')], 128.26 [C(4a)], 129.16 [C(8)], 129.21 [C(5'')], 130.00 [C(6'')], 137.47 [C(4)], 138.36 [C(3'')], 141.36 [C(1'')], 143.04 [C(8)], 147.35 [C(2)], 148.48 [C(1''')], 150.05 [C(6)], 150.39 [C(3''') + C(5''')].

2-Chloro-6-(4-(4-(pyridin-4-yl)benzyl)piperidin-1-yl)quinoline (130c)



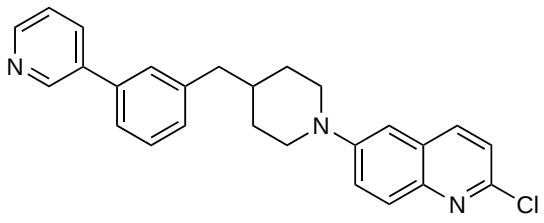
Using General Method 10, **118c** (75 mg, 0.30 mmol) and **24** (87 mg, 0.36 mmol) were reacted with $Pd(OAc)_2$ (0.3 mg, 1.3 μmol), CataCXium® A ligand (1.1 mg, 3.1 μmol) and sodium *tert*-butoxide (37 mg, 0.39 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with 2.5% methanol in dichloromethane gave **130c** as a yellow oil (69 mg, 56%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{26}H_{24}{}^{35}ClN_3/C_{26}H_{24}{}^{37}ClN_3$: 414.1737/416.1708; found 414.1732/416.1716. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [2H, qd, $^{2}J_{(3'/5')ax,(3'/5')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax} = {}^{3}J_{(3'/5')ax,4'ax}$ = 12.1 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 2.9 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.73-1.90 [3H, m, H(3'$_{eq}$) + H(4'$_{ax}$) + H(5'$_{eq}$)], 2.67 [2H, d, $^{3}J_{4'ax,A}$ = 6.8 Hz, H(A)], 2.79 [2H, td, $^{2}J_{(2'/6')ax,(2'/6')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax}$ = 12.1 Hz, $^{3}J_{(2'/6')ax,(3'/5')eq}$ = 2.0 Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 3.82 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.1 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 6.99 [1H, d, $^{4}J_{5,7}$ = 2.6 Hz, H(5)], 7.26 [1H, d, $^{3}J_{3,4}$ = 8.6 Hz, H(3)], 7.27-7.33 [2H, m, H(2'') + H(6'')], 7.45-7.55 [3H, m, H(7) + H(2''') + H(6''')], 7.56-7.64 [2H, m, H(3'') + H(5'')], 7.85 [1H, d, $^{3}J_{7,8}$ = 9.3 Hz, H(8)], 7.89 [1H, d, $^{3}J_{3,4}$ = 8.6 Hz, H(4)], 8.61-8.71 [2H, m, H(3''') + H(5''')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.98 [C(3') + C(5')], 37.96 [C(4')], 42.91 [C(A)], 49.80 [C(2') + C(6')], 109.00 [C(5)], 121.55 [C(2''') + C(6''')], 122.45 [C(3)], 123.75 [C(7)], 127.03 [C(3'') + C(5'')], 128.29 [C(4a)], 129.20 [C(8)], 130.06 [C(2'') + C(6'')], 136.00 [C(4'')], 137.50 [C(4)], 141.65 [C(1'')], 143.08 [C(8a)], 147.41 [C(2)], 148.21 [C(1''')], 150.09 [C(6)], 150.40 [C(3''') + C(5''')].

2-Chloro-6-(4-(2-(pyridin-3-yl)benzyl)piperidin-1-yl)quinoline (131a)



Using General Method 10, **119a** (79 mg, 0.31 mmol) and **24** (91 mg, 0.38 mmol) were reacted with $Pd(OAc)_2$ (0.4 mg, 1.8 μmol), CataCXium® A ligand (1.1 mg, 3.1 μmol) and sodium *tert*-butoxide (39 mg, 0.41 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **131a** as a yellow oil (43 mg, 33%). R_f = 0.27 (5% methanol in dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{26}H_{24}{}^{35}ClN_3/C_{26}H_{24}{}^{37}ClN_3$: 414.1737/416.1708; found 414.1729/416.1710. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ = 12.0 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.8 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.53 [1H, ttt, $^3J_{(3'/5')ax,4'ax}$ = 12.0 Hz, $^3J_{4'ax,A}$ = 7.3 Hz, $^3J_{(3'/5')eq,4'ax}$ = 3.7 Hz, H($4'_{ax}$)], 1.61 [2H, br d‡, $^2J_{(3'/5')ax,(3'/5')eq}$ = 12.0 Hz, H($3'_{eq}$) + H($5'_{eq}$)], 2.59-2.68 [4H, m, H(A) + H($2'_{ax}$) + H($6'_{ax}$)], 3.68 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.0 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 6.92 [1H, d, $^4J_{5,7}$ = 2.7 Hz, H(5)], 7.22 [1H, d, $^3J_{3'',4''}$ = 7.6 Hz, H(3'')], 7.25 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(3)], 7.28-7.40 [4H, m, H(4'') + H(5'') + H(6'') + H(5''')], 7.42 [1H, dd, $^3J_{7,8}$ = 9.3 Hz, $^4J_{5,7}$ = 2.7 Hz, H(7)], 7.64 [1H, dt, $^3J_{5''',6'''}$ = 7.7 Hz, $^4J_{2''',6'''} = {}^4J_{4''',6'''}$ = 1.4 Hz, H(6''')], 7.82 [1H, d, $^3J_{7,8}$ = 9.3 Hz, H(8)], 7.87 [1H, d, $^3J_{3,4}$ = 8.6 Hz, H(4)], 8.59 [1H, d, $^4J_{2''',6'''}$ = 1.4 Hz, H(2''')], 8.61 [1H, dd, $^3J_{4''',5'''}$ = 4.8 Hz, $^4J_{4''',6'''}$ = 1.4 Hz, H(4''')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.88 [C(3') + C(5')], 37.59 [C(4')], 39.76 [C(A)], 49.73 [C(2') + C(6')], 108.99 [C(5)], 122.41 [C(3)], 123.14 [C(5''')], 123.75 [C(7)], 126.41 [C(4'')], 128.24 [C(4a) + C(5'')], 129.14 [C(8)], 130.40 [C(6'')], 130.49 [C(3'')], 136.74 [C(6''')], 137.50 [C(4)], 137.65 [C(1''')], 138.14 [C(1'')], 138.63 [C(2'')], 143.06 [C(8a)], 147.37 [C(2)], 148.40 [C(4''')], 150.05 [C(6)], 150.21 [C(2''')].

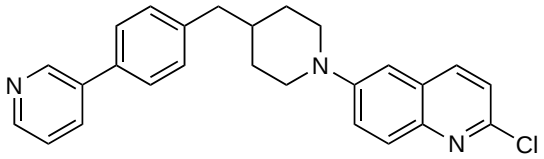
2-Chloro-6-(4-(3-(pyridin-3-yl)benzyl)piperidin-1-yl)quinoline (131b)



Using General Method 10, **119b** (113 mg, 0.45 mmol) and **24** (130 mg, 0.54 mmol) were

reacted with $Pd(OAc)_2$ (0.5 mg, 2.2 μmol), CataCXium® A ligand (1.6 mg, 4.5 μmol) and sodium *tert*-butoxide (56 mg, 0.58 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **131b** as a yellow oil (103 mg, 56%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{26}H_{24}{}^{35}ClN_3/C_{26}H_{24}{}^{37}ClN_3$: 414.1737/416.1708; found 414.1728/416.1710. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.3$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 3.1$ Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.74-1.88 [3H, m, H($3'_{eq}$) + H($4'_{ax}$) + H($5'_{eq}$)], 2.68 [2H, d, $^3J_{4'ax,A} = 6.8$ Hz, H(A)], 2.78 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = 12.3$ Hz, $^3J_{(2'/6')ax,(3'/5')eq} = 2.2$ Hz, H($2'_{ax}$) + H($6'_{ax}$)], 3.81 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.3$ Hz, H($2'_{eq}$) + H($6'_{eq}$)], 6.98 [1H, d, $^4J_{5,7} = 2.6$ Hz, H(5)], 7.20-7.28 [2H, m, H(3) + H(6'')], 7.34-7.50 [5H, m, H(7) +H(2'') + H(4'') + H(5'') + H(5''')], 7.82-7.91 [3H, m, H(4) + H(8) + H(6''')], 8.59 [1H, dd, $^3J_{4''',5'''} = 4.8$ Hz, $^4J_{4''',6'''} = 1.6$ Hz, H(4''')], 8.86 [1H, br d‡, $^4J_{2''',6'''} = 1.8$ Hz, H(2''')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.94 [C(3') + C(5')], 37.99 [C(4')], 43.23 [C(A)], 49.74 [C(2') + C(6')], 108.94 [C(5)], 122.39 [C(3)], 123.63 [C(5''')], 123.70 [C(7)], 125.02 [C(4'')], 128.04 [C(2'')], 128.26 [C(4a)], 129.04 [C(6'')], 129.14 [C(8)], 129.16 [C(5'')], 134.46 [C(6''')], 136.77 [C(1''')], 137.47 [C(4)], 138.02 [C(3'')], 141.29 [C(1'')], 143.02 [C(8a)], 147.32 [C(2)], 148.49 [C(2''')], 150.05 [C(6)].

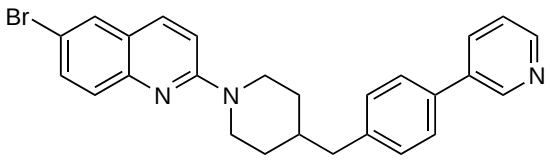
2-Chloro-6-(4-(4-(pyridin-3-yl)benzyl)piperidin-1-yl)quinoline (131c)



Using General Method 10, **119c** (75 mg, 0.30 mmol) and **24** (86 mg, 0.36 mmol) were reacted with $Pd(OAc)_2$ (0.3 mg, 1.5 μmol), CataCXium® A ligand (1.1 mg, 3.0 μmol) and sodium *tert*-butoxide (37 mg, 0.39 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **131c** as a yellow oil (32 mg, 26%), and impure **135c** as a yellow oil (31 mg, 23%).

*2-Chloro-6-(4-(4-(pyridin-3-yl)benzyl)piperidin-1-yl)quinoline (**131c**): $R_f = 0.20$* (2% methanol in dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{26}H_{24}{}^{35}ClN_3$/ $C_{26}H_{24}{}^{37}ClN_3$: 414.1737/416.1708; found 414.1729/416.1712. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.2$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 3.3$ Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.72-1.91 [3H, m, H($3'_{eq}$) + H($4'_{ax}$) + H($5'_{eq}$)], 2.66 [2H, d, $^3J_{4'ax,A} = 6.9$ Hz, H(A)], 2.79 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = 12.2$ Hz, $^3J_{(2'/6')ax,(3'/5')eq} = 1.8$ Hz, H($2'_{ax}$) + H($6'_{ax}$)], 3.82 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.2$ Hz, H($2'_{eq}$) + H($6'_{eq}$)], 6.99 [1H, d, $^4J_{5,7} = 2.6$ Hz, H(5)], 7.26 [1H, d, $^3J_{3,4} = 8.6$ Hz, H(3)], 7.27-7.32 [2H, m, H(2'') + H(6'')], 7.36 [1H, dd, $^3J_{5''',6'''} = 7.8$ Hz, $^3J_{4''',5'''} = 4.8$ Hz, H(5''')], 7.49 [1H, dd, $^3J_{7,8} = 9.3$ Hz, $^4J_{5,7} = 2.6$ Hz, H(7)], 7.51-7.56 [2H, m, H(3'') + H(5'')], 7.82-7.92 [3H, m, H(4)

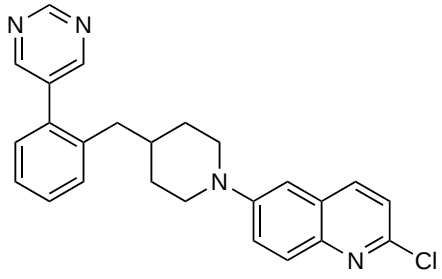
+ H(8) + H(6''')], 8.58 [1H, br d‡, $^{3}J_{4''',5'''}$ = 4.8 Hz, H(4''')], 8.86 [1H, d, $^{4}J_{2''',6'''}$ = 1.3 Hz, H(2''')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.97 [C(3') + C(5')], 37.97 [C(4')], 43.85 [C(A)], 49.79 [C(2') + C(6')], 108.97 [C(5)], 122.42 [C(3)], 123.66 [C(5''')], 123.74 [C(7)], 127.15 [C(3'') + C(5'')], 128.28 [C(4a)], 129.17 [C(8)], 130.01 [C(2'') + C(6'')], 134.26 [C(6''')], 135.71 [C(4'')], 136.55 [C(1''')], 137.49 [C(4)], 140.49 [C(1'')], 143.06 [C(8a)], 147.36 [C(2)], 148.36 [C(2''')], 148.45 [C(4''')], 150.09 [C(6)].



135c

*6-Bromo-2-(4-(4-(pyridin-3-yl)benzyl)piperidin-1-yl)quinoline (**135c**):* HRMS (ESI+) $[M+H]^+$ calcd. for $C_{26}H_{24}{}^{79}BrN_3/C_{26}H_{24}{}^{81}BrN_3$: 458.1232/460.1211; found 458.1219/ 460.1202. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 [2H, qd, $^{2}J_{(3'/5')ax,(3'/5')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax} = {}^{3}J_{(3'/5')ax,4'ax}$ = 12.7 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.8 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.76-1.95 [3H, m, H(3'$_{eq}$) + H(4'$_{ax}$) + H(5'$_{eq}$)], 2.63 [2H, d, $^{3}J_{4'ax,A}$ = 7.1 Hz, H(A)], 2.92 [2H, td, $^{2}J_{(2'/6')ax,(2'/6')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax}$ = 12.7 Hz, $^{3}J_{(2'/6')ax,(3'/5')eq}$ = 2.4 Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 4.54 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.7 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 6.98 [1H, d, $^{3}J_{3,4}$ = 9.2 Hz, H(3)], 7.25-7.30 [2H, m, H(2'') + H(6'')], 7.36 [1H, dd, $^{3}J_{5''',6'''}$ = 7.9 Hz, $^{3}J_{4''',5'''}$ = 4.8 Hz, H(5''')], 7.49-7.58 [4H, m, H(7) + H(8) + H(3'') + H(5'')], 7.70 [1H, d, $^{4}J_{5,7}$ = 1.9 Hz, H(5)], 7.74 [1H, d, $^{3}J_{3,4}$ = 9.2 Hz, H(4)], 7.87 [1H, dt, $^{3}J_{5''',6'''}$ = 7.9 Hz, $^{4}J_{2''',6'''} = {}^{4}J_{4''',6'''}$ = 1.7 Hz, H(6''')], 8.58 [1H, br d‡, $^{3}J_{4''',5'''}$ = 4.8 Hz, H(4''')], 8.85 [1H, br s‡, H(2''')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.11 [C(3') + C(5')], 38.59 [C(4')], 42.96 [C(A)], 45.63 [C(2') + C(6')], 110.68 [C(3)], 114.88 [C(6)], 123.68 [C(5''')], 124.10 [C(4a)], 127.15 [C(3'') + C(5'')], 128.36 [C(8)], 129.25 [C(5)], 130.03 [C(2'') + C(6'')], 132.66 [C(7)], 134.30 [C(6''')], 135.69 [C(4'')], 136.42 [C(4)], 136.60 [C(1''')], 140.55 [C(1'')], 146.94 [C(1'')], 146.94 [C(8a)], 148.36 [C(2''')], 148.43 [C(4''')], 157.52 [C(2)].

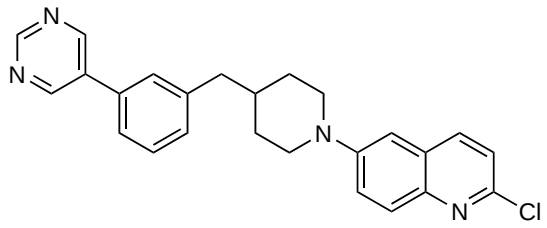
2-Chloro-6-(4-(2-(pyrimidin-5-yl)benzyl)piperidin-1-yl)quinoline (132a)



Using General Method 10, **120a** (74 mg, 0.29 mmol) and **24** (85 mg, 0.35 mmol) were reacted with $Pd(OAc)_2$ (0.3 mg, 1.5 μmol), CataCXium® A ligand (1.0 mg, 2.9 μmol) and

sodium *tert*-butoxide (36 mg, 0.38 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **132a** as a yellow oil (56 mg, 46%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{25}H_{23}{}^{35}ClN_4/C_{25}H_{23}{}^{37}ClN_4$: 415.1689/417.1660; found 415.1681/417.1663. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.1$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 3.6$ Hz, $H(3'_{ax}) + H(5'_{ax})$], 1.47-1.68 [3H, m, $H(3'_{eq}) + H(4'_{ax}) + H(5'_{eq})$], 2.57-2.70 [4H, m, H(A) + $H(2'_{ax}) + H(6'_{ax})$], 3.70 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.5$ Hz, $H(2'_{eq}) + H(6'_{eq})$], 6.92 [1H, d, $^4J_{5,7} = 2.6$ Hz, H(5)], 7.19-7.28 [2H, m, H(3) + H(3")], 7.31-7.38 [2H, m, H(4") + H(6")], 7.39-7.46 [2H, m, H(7) + H(5")], 7.82 [1H, d, $^3J_{7,8} = 9.3$ Hz, H(8)], 7.87 [1H, d, $^3J_{3,4} = 8.6$ Hz, H(4)], 8.73 [2H, s, H(2"') + H(6"')], 9.23 [1H, s, H(4"')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.85 [C(3') + C(5')], 37.72 [C(4')], 39.74 [C(A)], 49.68 [C(2') + C(6')], 109.04 [C(5)], 122.41 [C(3)], 123.71 [C(7)], 126.78 [C(4")], 128.21 [C(4a)], 129.10 [C(5")], 129.16 [C(8)], 130.48 [C(3")], 130.67 [C(6")], 134.72 [C(2")], 135.57 [C(1"')], 137.48 [C(4)], 138.25 [C(1")], 143.08 [C(8a)], 147.40 [C(2)], 149.94 [C(6)], 156.86 [C(2"') + C(6"')], 157.48 [C(4"')].

2-Chloro-6-(4-(3-(pyrimidin-5-yl)benzyl)piperidin-1-yl)quinoline (132b)

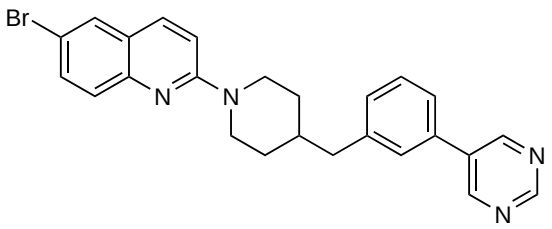


Using General Method 10, **120b** (58 mg, 0.23 mmol) and **24** (67 mg, 0.28 mmol) were reacted with $Pd(OAc)_2$ (0.3 mg, 1.3 μmol), CataCXium® A ligand (0.8 mg, 2.2 μmol) and sodium *tert*-butoxide (29 mg, 0.30 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **132b** as a yellow solid (57 mg, 60%), and a small amount of an impure mixture containing **136b** was also obtained.

*2-Chloro-6-(4-(3-(pyrimidin-5-yl)benzyl)piperidin-1-yl)quinoline (**132b**):* HRMS (ESI+) $[M+H]^+$ calcd. for $C_{25}H_{23}{}^{35}ClN_4/C_{25}H_{23}{}^{37}ClN_4$: 415.1689/417.1660; found 415.1684/417.1666. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 [2H, br qd‡, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.5$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 3.4$ Hz, $H(3'_{ax}) + H(5'_{ax})$], 1.73-1.90 [3H, m, $H(3'_{eq}) + H(4'_{ax}) + H(5'_{eq})$], 2.70 [2H, d, $^3J_{4'ax,A} = 7.7$ Hz, H(A)], 2.79 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = 12.5$ Hz, $^3J_{(2'/6')ax,(3'/5')eq} = 2.0$ Hz, $H(2'_{ax}) + H(6'_{ax})$], 3.82 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.5$ Hz, $H(2'_{eq}) + H(6'_{eq})$], 6.98 [1H, d, $^4J_{5,7} = 2.6$ Hz, H(5)], 7.25 [1H, d, $^3J_{3,4} = 8.7$ Hz, H(3)], 7.29 [1H, br d‡, $^3J_{5",6"} = 7.1$ Hz, H(6")], 7.38 [1H, br s‡, H(2")], 7.41-7.52 [3H, m, H(7) + H(4") + H(5")], 7.85 [1H, d, $^3J_{7,8} = 9.3$ Hz, H(8)], 7.89 [1H, d,

$^{3}J_{3,4}$ = 8.7 Hz, H(4)], 8.96 [2H, s, H(2''') + H(6''')], 9.21 [1H, s, H(4''')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.94 [C(3') + C(5')], 37.99 [C(4')], 43.18 [C(A)], 47.95 [C(2') + C(6')], 108.99 [C(5)], 122.43 [C(3)], 123.71 [C(7)], 124.88 [C(4'')], 127.83 [C(2'')], 128.26 [C(4a)], 129.19 [C(8)], 129.54 [C(5'')], 129.96 [C(6'')], 134.49 [*C(3'') or C(1''')], 134.50 [*C(3'') or C(1''')], 137.48 [C(4)], 141.78 [C(1'')], 143.06 [C(8a)], 147.39 [C(2)], 150.03 [C(6)], 155.06 [C(2''') + C(6''')], 157.63 [C(4''')].

*Some ^{13}C NMR signals could not be unambiguously assigned due to close proximity of chemical shifts.

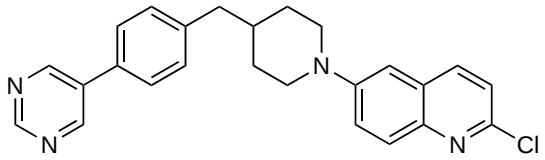


136b

*6-Bromo-2-(4-(3-(pyrimidin-5-yl)benzyl)piperidin-1-yl)quinoline (**136b**):* Obtained as an impure sample of **136b** and **132b** (approximately 5:2 by ^{1}H NMR analysis) by column chromatography. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{25}H_{23}{}^{79}BrN_4$/$C_{25}H_{23}{}^{81}BrN_4$: 459.1184/461.1164; found 459.1173/461.1157. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 [1.5H, br qd‡, $^{2}J_{(3'/5')ax,(3'/5')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = $^{3}J_{(3'/5')ax,4'ax}$ = 12.5 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.4 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.49 [0.5H, br qd‡, $^{2}J_{(*3'/*5')ax,(*3'/*5')eq}$ = $^{3}J_{(*2'/*6')ax,(*3'/*5')ax}$ = $^{3}J_{(*3'/5')ax,*4'ax}$ = 12.5 Hz, $^{3}J_{(*2'/*6')eq,(*3'/*5')ax}$ = 3.4 Hz, *H(3'$_{ax}$) + *H(5'$_{ax}$)], 1.73-1.96 [3H, m, H(3'$_{eq}$) + H(4'$_{ax}$) + H(5'$_{eq}$) + *H(3'$_{eq}$) + *H(4'$_{ax}$) + *H(5'$_{eq}$)], 2.64-2.74 [2H, m, H(A) + *H(A)], 2.79 [0.5H, td, $^{2}J_{(*2'/*6')ax,(*2'/*6')eq}$ = $^{3}J_{(*2'/*6')ax,(*3'/*5')ax}$ = 12.5 Hz, $^{3}J_{(*2'/*6')ax,(*3'/*5')eq}$ = 2.0 Hz, *H(2'$_{ax}$) + *H(6'$_{ax}$)], 2.91 [1.5H, td, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = 12.5 Hz, $^{3}J_{(2'/6')ax,(3'/5')eq}$ = 2.2 Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 3.82 [0.5H, br d‡, $^{2}J_{(*2'/*6')ax,(*2'/*6')eq}$ = 12.5 Hz, *H(2'$_{eq}$) + *H(6'$_{eq}$)], 4.55 [1.5H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.5 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 6.95-7.01 [1H, m, H(3) + *H(5)], 7.24-7.32 [1.25H, m, H(6'') + *H(5) + *H(6'')], 7.35-7.40 [1H, m, H(2'') + *H(2'')], 7.41-7.50 [2.25H, m, H(4'') + H(5'') + *H(7) + *H(4'') + *H(5'')], 7.52 and 7.55 [1.5H, *ABX*, *A*:d, *B*:dd, $^{3}J_{7,8}$(J_{AB}) = 8.9 Hz, $^{3}J_{5,7}$(J_{BX}) = 2.1 Hz, H(8) + H(7)], 7.70 [0.75H, d, $^{3}J_{5,7}$ = 2.1 Hz, H(5)], 7.75 [0.75H, d, $^{3}J_{7,8}$ = 9.2 Hz, H(4)], 8.93-8.99 [2H, m, H(2''') + H(6''') + *H(2''') + *H(6''')], 9.18-9.24 [1H, s, H(4''') + *H(4''')].

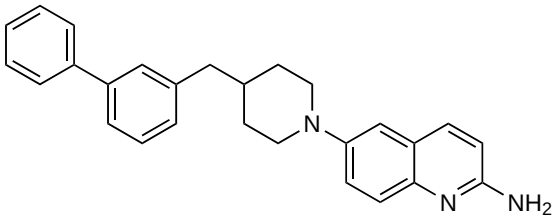
*denotes signals corresponding to **132b**.

2-Chloro-6-(4-(4-(pyrimidin-5-yl)benzyl)piperidin-1-yl)quinoline (132c)



Using General Method 10, **120c** (63 mg, 0.25 mmol) and **24** (72 mg, 0.30 mmol) were reacted with $Pd(OAc)_2$ (0.3 mg, 1.2 μmol), CataCXium® A ligand (0.9 mg, 2.5 μmol) and sodium *tert*-butoxide (31 mg, 0.32 mmol) in (trifluoromethyl)benzene (2 mL). Work-up as specified and column chromatography on silica gel eluting with dichloromethane gave **132c** as a yellow oil (37 mg, 36%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{25}H_{23}{}^{35}ClN_4/C_{25}H_{23}{}^{37}ClN_4$: 415.1689/417.1660; found 415.1681/417.1662. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.2$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 2.9$ Hz, $H(3'_{ax}) + H(5'_{ax})$], 1.74-1.90 [3H, m, $H(3'_{eq}) + H(4'_{ax}) + H(5'_{eq})$], 2.68 [2H, d, $^3J_{4'ax,A} = 6.8$ Hz, H(A)], 2.79 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = 12.2$ Hz, $^3J_{(2'/6')ax,(3'/5')eq} = 1.6$ Hz, $H(2'_{ax}) + H(6'_{ax})$], 3.83 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.2$ Hz, $H(2'_{eq}) + H(6'_{eq})$], 6.99 [1H, d, $^4J_{5,7} = 2.6$ Hz, H(5)], 7.26 [1H, d, $^3J_{3,4} = 8.6$ Hz, H(3)], 7.31-7.37 [2H, m, H(2'') + H(6'')], 7.49 [1H, dd, $^3J_{7,8} = 9.3$ Hz, $^4J_{5,7} = 2.6$ Hz, H(7)], 7.50-7.56 [2H, m, H(3'') + H(5'')], 7.85 [1H, d, $^3J_{7,8} = 9.3$ Hz, H(8)], 7.90 [1H, d, $^3J_{3,4} = 8.6$ Hz, H(4)], 8.96 [2H, s, H(2''') + H(6''')], 9.20 [1H, s, H(4''')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.96 [C(3') + C(5')], 37.96 [C(4')], 42.88 [C(A)], 49.79 [C(2') + C(6')], 109.01 [C(5)], 122.45 [C(3)], 123.74 [C(7)], 127.02 [C(3'') + C(5'')], 128.27 [C(4a)], 129.20 [C(8)], 130.37 [C(2'') + C(6'')], 132.15 [C(4'')], 134.27 [C(1''')], 137.49 [C(4)], 141.59 [C(1'')], 143.08 [C(8a)], 147.41 [C(2)], 150.06 [C(6)], 154.89 [C(2''') + C(6''')], 157.48 [C(4''')].

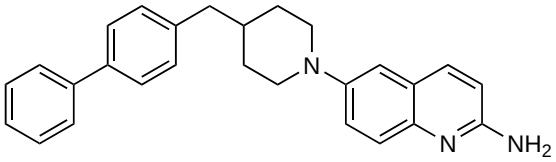
6-(4-((1,1'-Biphenyl)-3-ylmethyl)piperidin-1-yl)quinolin-2-amine (113a)



Using General Method 11, **129a** (96 mg, 0.23 mmol) was treated with LiHMDS solution (1.0 M in THF, 511 μL, 0.51 mmol), $Pd(dba)_2$ (1.3 mg, 2.3 μmol) and DavePhos (1.1 mg, 2.8 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 9:1 dichloromethane/methanol gave **113a** as a brown solid (40 mg, 44%). $R_f = 0.25$ (1:9 methanol/dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{27}H_{27}N_3$: 394.2283; found 394.2279. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq}$

$= {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.5$ Hz, ${}^3J_{(2'/6')eq,(3'/5')ax} = 3.8$ Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.75 [1H, ttt, ${}^3J_{(3'/5')ax,4'ax} = 12.5$ Hz, ${}^3J_{4'ax,A} = 7.4$ Hz, ${}^3J_{(3'/5')eq,4'ax} = 3.8$ Hz, H($4'_{ax}$)], 1.83 [2H, br d‡, ${}^2J_{(3'/5')ax,(3'/5')eq} = 12.5$ Hz, H($3'_{eq}$) + H($5'_{eq}$)], 2.64-2.75 [2H, m, H(A)+ H($2'_{ax}$) + H($6'_{ax}$)], 3.69 [2H, br d‡, ${}^2J_{(2'/6')ax,(2'/6')eq} = 12.5$ Hz, H($2'_{eq}$) + H($6'_{eq}$)], 5.23 [2H, br s, NH_2], 6.70 [1H, d, ${}^3J_{3,4} = 8.9$ Hz, H(3)], 6.96 [1H, d, ${}^4J_{5,7} = 2.6$ Hz, H(5)], 7.16 [1H, br d‡, ${}^3J_{5'',6''} = 7.1$ Hz, H(6'')], 7.32-7.49 [7H, m, H(7) + H(2'') + H(4'') + H(5'') + H(3''') + H(4''') + H(5''')], 7.55-7.64 [3H, m, H(4) + H(2''') + H(6''')], 7.79 [1H, d, ${}^3J_{7,8} = 8.9$ Hz, H(8)].

6-(4-((1,1'-Biphenyl)-4-ylmethyl)piperidin-1-yl)quinolin-2-amine (113b)



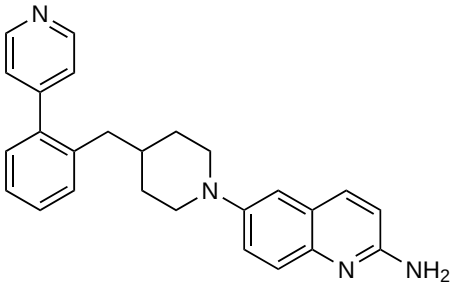
Using General Method 11, **129b** (78 mg, 0.19 mmol) was treated with LiHMDS solution (1.0 M in THF, 418 μL, 0.42 mmol), $Pd(dba)_2$ (1.1 mg, 1.9 μmol) and DavePhos (0.9 mg, 2.3 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **113b** as a brown solid (40 mg, 54%). $R_f = 0.23$ (1:9 methanol/dichloromethane). MP: 169-173°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{27}H_{27}N_3$: 394.2283; found 394.2274. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 [2H, qd, ${}^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 11.8$ Hz, ${}^3J_{(2'/6')eq,(3'/5')ax} = 3.5$ Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.74 [1H, ttt, ${}^3J_{(3'/5')ax,4'ax} = 11.8$ Hz, ${}^3J_{4'ax,A} = 7.2$ Hz, ${}^3J_{(3'/5')eq,4'ax} = 3.5$ Hz, H($4'_{ax}$)], 1.84 [2H, br d‡, ${}^2J_{(3'/5')ax,(3'/5')eq} = 11.8$ Hz, H($3'_{eq}$) + H($5'_{eq}$)], 2.65 [2H, d, ${}^3J_{4'ax,A} = 7.2$ Hz, H(A)], 2.70 [2H, td, ${}^2J_{(2'/6')ax,(2'/6')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = 11.8$ Hz, ${}^3J_{(2'/6')ax,(3'/5')eq} = 1.7$ Hz, H($2'_{ax}$) + H($6'_{ax}$)], 3.69 [2H, br d‡, ${}^2J_{(2'/6')ax,(2'/6')eq} = 11.8$ Hz, H($2'_{eq}$) + H($6'_{eq}$)], 4.84 [2H, br s, NH_2], 6.67 [1H, d, ${}^3J_{3,4} = 8.8$ Hz, H(3)], 6.96 [1H, d, ${}^4J_{5,7} = 2.6$ Hz, H(5)], 7.21-7.29 [2H, m, H(2'') + H(6'')], 7.30-7.39 [2H, m, H(7) + H(4''')], 7.39-7.47 [2H, m, H(3''') + H(5''')], 7.49-7.56 [2H, m, H(3'') + H(5'')], 7.55-7.62 [3H, m, H(8) + H(2''') + H(6''')], 7.77 [1H, d, ${}^3J_{3,4} = 8.8$ Hz, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.32 [C(3') + C(5')], 37.98 [C(4')], 42.94 [C(A)], 50.95 [C(2') + C(6')], 111.36 [C(5)], 111.92 [C(3)], 123.78 [C(7)], 124.28 [C(4a)], 126.25 [br, C(8)], 127.12 [*C(2''') + *C(6''')], 127.13 [*C(3'') + *C(5'')], 127.20 [C(4''')], 128.87 [C(3''') + C(5''')], 129.72 [C(2'') + C(6'')], 137.70 [br, C(4)], 139.04 [C(4'')], 139.73 [C(1'')], 141.19 [C(1''')], **141.96 [C(8a)], 147.89 [C(6)], 155.37 [C(2)].

*Some ^{13}C NMR signals could not be unambiguously assigned due to close proximity of chemical shifts.

**The C(8a) signal was not observed in the ^{13}C NMR spectrum, and the chemical shift was

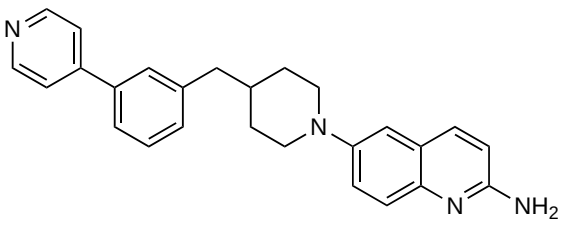
instead determined using clear [^{1}H,^{13}C]-HMBC spectrum correlations with the H(4) and H(5) signals.

6-(4-(2-(Pyridin-4-yl)benzyl)piperidin-1-yl)quinolin-2-amine (114a)



Using General Method 11, **130a** (88 mg, 0.21 mmol) was treated with LiHMDS solution (1.0 M in THF, 470 μL, 0.47 mmol), Pd(dba)$_2$ (1.2 mg, 2.1 μmol) and DavePhos (0.9 mg, 2.3 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **114a** as a yellow solid (46 mg, 55%). MP: degraded 180°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{26}H_{26}N_4$: 395.2236; found 395.2241. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 [2H, qd, $^{2}J_{(3'/5')ax,(3'/5')eq} = {}^{3}J_{(2'/6')ax,(3'/5')ax} = {}^{3}J_{(3'/5')ax,4'ax}$ = 12.2 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.5 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.41-1.54 [1H, m, H(4'$_{ax}$)], 1.60 [2H, br d‡, $^{2}J_{(3'/5')ax,(3'/5')eq}$ = 12.2 Hz, H(3'$_{eq}$) + H(5'$_{eq}$)], 2.55 [2H, br t‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = 12.2 Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 2.63 [2H, d, $^{3}J_{4'ax,A}$ = 7.1 Hz, H(A)], 3.57 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.2 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 5.03 [2H, br s, NH_2], 6.69 [1H, d, $^{3}J_{3,4}$ = 8.8 Hz, H(3)], 6.90 [1H, d, $^{4}J_{5,7}$ = 2.2 Hz, H(5)], 7.19 [1H, br d‡, $^{3}J_{3'',4''}$ = 7.5 Hz, H(3'')], 7.23-7.34 [5H, m, H(7) + H(4'') + H(5'') + H(6'') + H(2''') + H(6''')], 7.37 [1H, t, $^{3}J_{4'',5''} = {}^{3}J_{5'',6''}$ = 7.40 Hz, H(5'')], 7.55 [1H, d, $^{3}J_{7,8}$ = 9.1 Hz, H(8)], 7.75 [1H, d, $^{3}J_{3,4}$ = 8.8 Hz, H(4)], 8.63-8.69 [2H, m, H(3''') + H(5''')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.16 [C(3') + C(5')], 37.53 [C(4')], 39.70 [C(A)], 50.80 [C(2') + C(6')], 111.43 [C(5)], 112.00 [C(3)], 123.85 [C(7)], 124.09 [C(4a)], 124.62 [C(2''') + C(6''')], 125.66 [C(4'')], 126.35 [C(8)], 128.40 [C(5'')], 129.71 [C(3'')], 130.46 [C(6'')], 137.60 [C(4)], 138.04 [C(1'')], 139.71 [C(2'')], 141.04 [br, C(8a)], 147.91 [C(6)], 149.79 [C(3''') + C(5''')], 150.17 [C(1''')], 155.17 [C(2)].

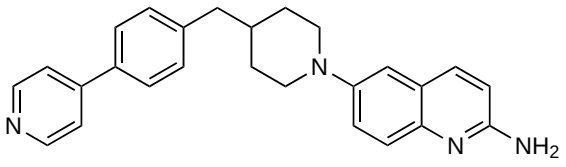
6-(4-(3-(Pyridin-4-yl)benzyl)piperidin-1-yl)quinolin-2-amine (114b)



Using General Method 11, **130b** (72 mg, 0.17 mmol) was treated with LiHMDS solution (1.0

M in THF, 385 μL, 0.38 mmol), $Pd(dba)_2$ (1.0 mg, 1.7 μmol) and DavePhos (0.8 mg, 2.0 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **114b** as a yellow powder (22 mg, 32%). MP: 230-233°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{26}H_{26}N_4$: 395.2236; found 395.2229. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51 [2H, dq, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ = 12.3 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.9 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.69-1.88 [3H, m, H($3'_{eq}$) + H($4'_{ax}$) + H($5'_{eq}$)], 2.60-2.84 [4H, m, H(A) + H($2'_{ax}$) + H($6'_{ax}$)], 3.69 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.3 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 4.93 [2H, br s, NH_2], 6.68 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.98 [1H, d, $^4J_{5,7}$ = 2.7 Hz, H(5)], 7.27 [1H, br d‡, $^3J_{5'',6''}$ = 7.4 Hz, H(6'')], 7.36 [1H, dd, $^3J_{7,8}$ = 9.2 Hz, $^4J_{5,7}$ = 2.7 Hz, H(7)], 7.39-7.46 [2H, m, H(2'') + H(5'')], 7.47-7.55 [3H, m, H(4'') + H(2''') + H(6''')], 7.58 [1H, d, $^3J_{7,8}$ = 9.2 Hz, H(8)], 7.77 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)], 8.63-8.70 [2H, m, H(3''') + H(5''')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.26 [C(3') + C(5')], 38.01 [C(4')], 43.31 [C(A)], 50.88 [C(2') + C(6')], 111.39 [C(5)], 111.96 [C(3)], 121.84 [C(2''') + C(6''')], 123.78 [C(7)], 124.22 [C(4a)], 124.85 [C(4'')], 126.09 [C(8)], 127.91 [C(2'')], 129.19 [C(5'')], 130.06 [C(6'')], 137.82 [C(4)], 138.35 [C(3'')], 141.58 [C(8a) + C(1'')], 147.85 [C(6)], 148.58 [C(1''')], 150.39 [C(3''') + C(5''')], 155.32 [C(2)].

6-(4-(4-(Pyridin-4-yl)benzyl)piperidin-1-yl)quinolin-2-amine (114c)

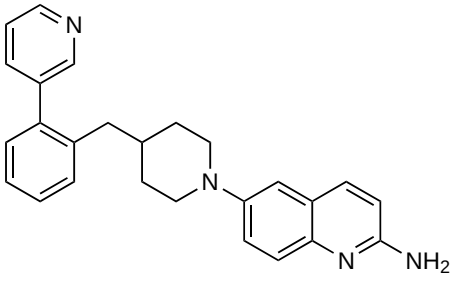


Using General Method 11, **130c** (57 mg, 0.14 mmol) was treated with LiHMDS solution (1.0 M in THF, 300 μL, 0.30 mmol), $Pd(dba)_2$ (0.8 mg, 1.4 μmol) and DavePhos (0.7 mg, 1.8 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **114c** as a yellow solid (29 mg, 54%). MP: degraded 255°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{26}H_{26}N_4$: 395.2236; found 395.2234. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ = 12.0 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.4 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.69-1.88 [3H, m, H($3'_{eq}$) + H($4'_{ax}$) + H($5'_{eq}$)], 2.63-2.77 [4H, m, H(A) + H($2'_{ax}$) + H($6'_{ax}$)], 3.70 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.0 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 4.92 [2H, br s, NH_2], 6.69 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.97 [1H, d, $^4J_{5,7}$ = 2.5 Hz, H(5)], 7.28-7.33 [2H, m, H(2'') + H(6'')], 7.36 [1H, dd, $^3J_{7,8}$ = 9.1 Hz, $^4J_{5,7}$ = 2.5 Hz, H(7)], 7.48-7.54 [2H, m, H(2''') + H(6''')], 7.56-7.64 [3H, m, H(8) + H(3'') + H(5'')], 7.78 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)], 8.62-8.68 [2H, m, H(3''') + H(5''')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.27 [C(3') + C(5')], 37.93 [C(4')], 42.97 [C(A)], 50.87 [C(2') + C(6')], 111.39 [C(5)], 111.97 [C(3)], 121.57 [C(2''') + C(6''')], 123.82 [C(7)], 124.21 [C(4a)], 125.99 [C(8)], 127.00 [C(3'') + C(5'')], 130.08 [C(2'') + C(6'')], 135.93 [C(4'')], 137.92 [C(4)], *141.42 [C(8a)], 141.86 [C(1'')], 147.91 [C(6)], 148.27 [C(1''')], 150.40 [C(3''') +

C(5‴)], 155.24 [C(2)].

*The C(8a) signal was not observed in the ^{13}C NMR spectrum, and the chemical shift was instead determined using clear [^{1}H,^{13}C]-HMBC spectrum correlations with the H(4), H(5) and H(7) signals.

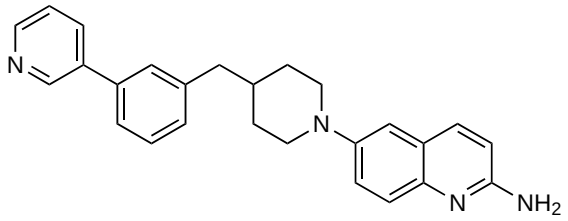
6-(4-(2-(Pyridin-3-yl)benzyl)piperidin-1-yl)quinolin-2-amine (115a)



Using General Method 11, **131a** (33 mg, 0.08 mmol) was treated with LiHMDS solution (1.0 M in THF, 175 μL, 0.18 mmol), Pd(dba)$_2$ (0.5 mg, 0.9 μmol) and DavePhos (0.4 mg, 1.0 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 9:1 dichloromethane/methanol gave **115a** as a yellow oil (21 mg, 67%). R_f = 0.31 (10% methanol in dichloromethane). HRMS (ESI+) [M+H]$^+$ calcd. for $C_{26}H_{26}N_4$: 395.2236; found 395.2228. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq}$ = $^3J_{(2'/6')ax,(3'/5')ax}$ = $^3J_{(3'/5')ax,4'ax}$ = 12.0 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.5 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.48 [1H, ttt, $^3J_{(3'/5')ax,4'ax}$ = 12.0 Hz, $^3J_{4'ax,A}$ = 7.3 Hz, $^3J_{(3'/5')eq,4'ax}$ = 3.8 Hz, H(4'$_{ax}$)], 1.60 [2H, br d‡, $^2J_{(3'/5')ax,(3'/5')eq}$ = 12.0 Hz, H(3'$_{eq}$) + H(5'$_{eq}$)], 2.55 [2H, td, $^2J_{(2'/6')ax,(2'/6')eq}$ = $^3J_{(2'/6')ax,(3'/5')ax}$ = 12.0 Hz, $^3J_{(2'/6')ax,(3'/5')eq}$ = 1.7 Hz, H(2'$_{ax}$) + H(6'$_{ax}$)], 2.62 [2H, d, $^3J_{4'ax,A}$ = 7.3 Hz, H(A)], 3.56 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.0 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 5.06 [2H, br s, NH_2], 6.66 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.89 [1H, d, $^4J_{5,7}$ = 2.5 Hz, H(5)], 7.21 [1H, d, $^3J_{3'',4''}$ = 7.5 Hz, H(3'')], 7.27-7.39 [5H, m, H(7) + H(4'') + H(5'') + H(6'') + H(5‴)], 7.55 [1H, d, $^3J_{7,8}$ = 9.1 Hz, H(8)], 7.64 [1H, br d‡, $^3J_{5''',6'''}$ = 7.8 Hz, H(6‴)], 7.74 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)], 8.57-8.62 [2H, m, H(2‴) + H(4‴)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.16 [C(3') + C(5')], 37.58 [C(4')], 39.79 [C(A)], 50.83 [C(2') + C(6')], 111.44 [C(5)], 112.01 [C(3)], 123.12 [C(5‴)], 123.83 [C(7)], 124.09 [C(4a)], 125.76 [C(8)], 126.33 [C(4'')], 128.21 [C(5'')], 130.41 [C(6'')], 130.45 [C(3'')], 136.77 [C(6‴)], 137.70 [C(1‴)], 137.94 [C(4)], 138.33 [C(1'')], 138.64 [C(2'')], *141.17 [C(8a)], 147.86 [C(6)], 148.36 [C(4‴)], 150.23 [C(2‴)], 155.30 [C(2)].

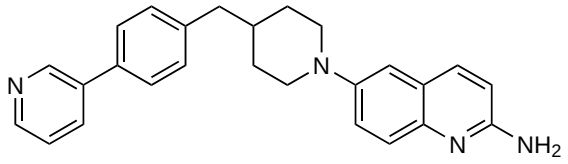
*The C(8a) signal was not observed in the ^{13}C NMR spectrum, and the chemical shift was instead determined using clear [^{1}H,^{13}C]-HMBC spectrum correlations with the H(4) and H(5) signals.

6-(4-(3-(Pyridin-3-yl)benzyl)piperidin-1-yl)quinolin-2-amine (115b)



Using General Method 11, **131b** (100 mg, 0.24 mmol) was treated with LiHMDS solution (1.0 M in THF, 530 μL, 0.53 mmol), $Pd(dba)_2$ (1.4 mg, 2.4 μmol) and DavePhos (1.1 mg, 2.8 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **115b** as a yellow oil (56 mg, 59%). MP: degraded 160°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{26}H_{26}N_4$: 395.2236; found 395.2230. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ = 12.1 Hz, $^3J_{(2'/6')eq,(3'/5')ax}$ = 3.4 Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.68-1.89 [3H, m, H(3'$_{eq}$) + H(4'$_{ax}$) + H(5'$_{eq}$)], 2.61-2.76 [4H, m, H(A) + H(2'$_{ax}$) + H(6'$_{ax}$)], 3.69 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq}$ = 12.1 Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 4.71 [2H, br s, NH_2], 6.66 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(3)], 6.96 [1H, d, $^4J_{5,7}$ = 2.5 Hz, H(5)], 7.23 [1H, br d‡, $^3J_{5'',6''}$ = 6.7 Hz, H(6'')], 7.31-7.41 [5H, m, H(7) + H(2'') + H(4'') + H(5'') + H(5''')], 7.56 [1H, d, $^3J_{7,8}$ = 9.2 Hz, H(8)], 7.75 [1H, d, $^3J_{3,4}$ = 8.8 Hz, H(4)], 7.88 [1H, br d‡, $^3J_{5''',6'''}$ = 7.9 Hz, H(6''')], 8.59 [1H, d, $^3J_{4''',5'''}$ = 4.7 Hz, H(4''')], 8.86 [1H, d, $^4J_{2''',6'''}$ = 2.0 Hz, H(2''')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.26 [C(3') + C(5')], 37.98 [C(4')], 43.31 [C(A)], 50.91 [C(2') + C(6')], 111.37 [C(5)], 111.88 [C(3)], 123.63 [C(5''')], 123.67 [C(7)], 124.30 [C(4a)], 124.95 [C(4'')], 126.48 [C(8)], 128.08 [C(2'')], 129.08 [C(6'')], 129.12 [C(5'')], 134.49 [C(6''')], 136.84 [C(1''')], 137.47 [C(4)], 137.99 [C(3'')], 141.51 [C(1'')], 142.35 [C(8a)], 147.72 [C(6)], 148.52 [C(2''')], 148.58 [C(4''')], 155.46 [C(2)].

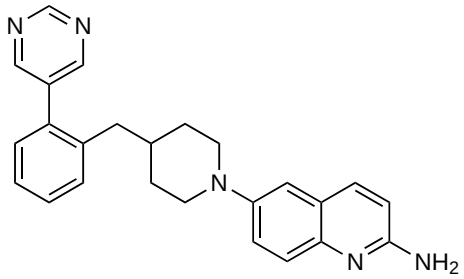
6-(4-(4-(Pyridin-3-yl)benzyl)piperidin-1-yl)quinolin-2-amine (115c)



Using General Method 11, **131c** (20 mg, 0.05 mmol) was treated with LiHMDS solution (1.0 M in THF, 106 μL, 0.11 mmol), $Pd(dba)_2$ (0.3 mg, 0.5 μmol) and DavePhos (0.2 mg, 0.6 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **115c** as a yellow solid (12 mg, 63%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{26}H_{26}N_4$: 395.2236; found 395.2230. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax}$ =

12.1 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.4 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.74 [1H, ttt, $^{3}J_{(3'/5')ax,4'ax}$ = 12.1 Hz, $^{3}J_{4'ax,A}$ = 7.0 Hz, $^{3}J_{(3'/5')eq,(4'ax}$ = 3.4 Hz, H($4'_{ax}$)], 1.83 [2H, br d‡, $^{2}J_{(3'/5')ax,(3'/5')eq}$ = 12.1 Hz, H($3'_{eq}$) + H($5'_{eq}$)], 2.63-2.75 [4H, m, H(A) + H($2'_{ax}$) + H($6'_{ax}$)], 3.70 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.1 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 4.80 [2H, br s, NH_2], 6.67 [1H, d, $^{3}J_{3,4}$ = 8.8 Hz, H(3)], 6.97 [1H, d, $^{4}J_{5,7}$ = 2.6 Hz, H(5)], 7.27-7.33 [2H, m, H(2") + H(6")], 7.33-7.39 [2H, m, H(7) + H(5"')], 7.49-7.55 [2H, m, H(3") + H(5")], 7.58 [1H, d, $^{3}J_{7,8}$ = 9.2 Hz, H(8)], 7.77 [1H, d, $^{3}J_{3,4}$ = 8.8 Hz, H(4)], 7.87 [1H, ddd, $^{3}J_{5''',6'''}$ = 7.9 Hz, $^{4}J_{2''',6'''}$ = 2.0 Hz, $^{4}J_{4''',6'''}$ = 1.5 Hz, H(6"')], 8.58 [1H, dd, $^{3}J_{4''',5'''}$ = 4.7 Hz, $^{4}J_{4''',6'''}$ = 1.5 Hz, H(4"')], 8.86 [1H, d, $^{4}J_{2''',6'''}$ = 2.0 Hz, H(2"')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.29 [C(3') + C(5')], 37.96 [C(4')], 42.94 [C(A)], 50.93 [C(2') + C(6')], 111.38 [C(5)], 111.92 [C(3)], 123.66 [C(5"')], 123.76 [C(7)], 124.29 [C(4a)], 126.33 [br, C(8)], 127.14 [C(3") + C(5")], 130.05 [C(2") + C(6")], 134.28 [br, C(6"')], 135.65 [C(4")], 136.61 [C(1"')], 137.65 [br, C(4)], 140.73 [C(1")], 142.05 [br, C(8a)], 147.83 [C(6)], 148.39 [C(2"')], 148.44 [C(4"')], 155.39 [C(2)].

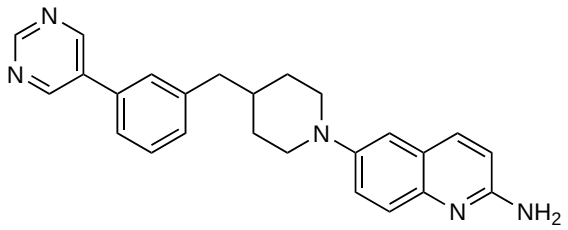
6-(4-(2-(Pyrimidin-5-yl)benzyl)piperidin-1-yl)quinolin-2-amine (116a)



Using General Method 11, **132a** (46 mg, 0.11 mmol) was treated with LiHMDS solution (1.0 M in THF, 244 μL, 0.22 mmol), $Pd(dba)_2$ (0.6 mg, 1.0 μmol) and DavePhos (0.5 mg, 1.3 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **116a** as a yellow solid (23 mg, 52%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{25}H_{25}N_5$: 396.2188; found 396.2182. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 [2H, qd, $^{2}J_{(3'/5')ax,(3'/5')eq}$ = $^{3}J_{(2'/6')ax,(3'/5')ax}$ = $^{3}J_{(3'/5')ax,4'ax}$ = 12.0 Hz, $^{3}J_{(2'/6')eq,(3'/5')ax}$ = 3.8 Hz, H($3'_{ax}$) + H($5'_{ax}$)], 1.49 [1H, ttt, $^{3}J_{(3'/5')ax,4'ax}$ = 12.0 Hz, $^{3}J_{4'ax,A}$ = 7.6 Hz, $^{3}J_{(3'/5')eq,(4'ax}$ = 3.8 Hz, H($4'_{ax}$)], 1.62 [2H, br d‡, $^{2}J_{(3'/5')ax,(3'/5')eq}$ = 12.0 Hz, H($3'_{eq}$) + H($5'_{eq}$)], 2.50-2.65 [4H, m, H($2'_{ax}$) + H($6'_{ax}$) + H(A)], 3.57 [2H, br d‡, $^{2}J_{(2'/6')ax,(2'/6')eq}$ = 12.0 Hz, H($2'_{eq}$) + H($6'_{eq}$)], 4.80 [2H, br s, NH_2], 6.66 [1H, d, $^{3}J_{3,4}$ = 8.8 Hz, H(3)], 6.90 [1H, d, $^{4}J_{5,7}$ = 2.6 Hz, H(5)], 7.21 [1H, br d‡, $^{3}J_{3'',4''}$ = 7.1 Hz, H(3")], 7.29 [1H, dd, $^{3}J_{7,8}$ = 9.2 Hz, $^{4}J_{5,7}$ = 2.6 Hz, H(7)], 7.32-7.39 [2H, m, H(4") + H(6")], 7.42 [1H, t, $^{3}J_{4'',5''}$ = $^{3}J_{5'',6''}$ = 7.5 Hz, H(5")], 7.54 [1H, d, $^{3}J_{7,8}$ = 9.2 Hz, H(8)], 7.74 [1H, d, $^{3}J_{3,4}$ = 8.8 Hz, H(4)], 8.75 [2H, s, H(2"') + H(6"')], 9.23 [1H, s, H(4"')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.16 [C(3') + C(5')], 37.73 [C(4')], 39.80 [C(A)], 50.84 [C(2') + C(6')], 111.49 [C(5)], 111.90 [C(3)], 123.74 [C(7)], 124.21 [C(4a)], 126.30 [C(8)], 126.70 [C(4")], 129.08 [C(5")], 130.45 [C(3")], 130.71 [C(6")], 134.73 [C(2")], 135.63 [C(1"')], 137.63 [C(4)], 138.48 [C(1")],

142.08 [C(8a)], 147.66 [C(6)], 155.40 [C(2)], 156.89 [C(2''') + C(6''')], 157.45 [C(4''')].

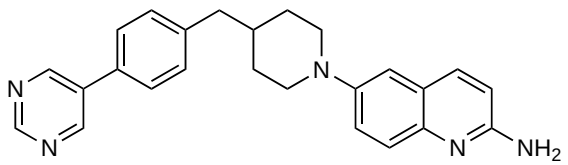
6-(4-(3-(Pyrimidin-5-yl)benzyl)piperidin-1-yl)quinolin-2-amine (116b)



Using General Method 11, **132b** (37 mg, 0.09 mmol) was treated with LiHMDS solution (1.0 M in THF, 200 μL, 0.20 mmol), $Pd(dba)_2$ (0.5 mg, 0.9 μmol) and DavePhos (0.4 mg, 1.0 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **116b** as a yellow oil (13 mg, 37%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{25}H_{25}N_5$: 396.2188; found 396.2185. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.1$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 3.3$ Hz, $H(3'_{ax}) + H(5'_{ax})$], 1.70-1.88 [3H, m, $H(3'_{eq}) + H(4'_{ax}) + H(5'_{eq})$], 2.65-2.77 [4H, m, $H(2'_{ax}) + H(6'_{ax}) + H(A)$], 3.70 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.1$ Hz, $H(2'_{eq}) + H(6'_{eq})$], 5.07 [2H, br s, NH_2], 6.70 [1H, d, $^3J_{3,4} = 8.8$ Hz, H(3)], 6.96 [1H, d, $^4J_{5,7} = 2.6$ Hz, H(5)], 7.29 [1H, br d‡, $^3J_{5'',6''} = 7.1$ Hz, H(6'')], 7.36 [1H, dd, $^3J_{7,8} = 9.2$ Hz, $^4J_{5,7} = 2.6$ Hz, H(7)], 7.39 [1H, br s‡, H(2'')], 7.41-7.50 [2H, m, H(4'') + H(5'')], 7.58 [1H, d, $^3J_{7,8} = 9.2$ Hz, H(8)], 7.78 [1H, d, $^3J_{3,4} = 8.8$ Hz, H(4)], 8.96 [2H, s, H(2''') + H(6''')], 9.21 [1H, s, H(4''')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.22 [C(3') + C(5')], 37.97 [C(4')], 43.25 [C(A)], 50.81 [C(2') + C(6')], 111.42 [C(5)], 112.04 [C(3)], 123.85 [C(7)], 124.12 [C(4a)], 124.84 [C(4'')], 125.68 [br, C(8)], 127.88 [C(2'')], 129.52 [C(5'')], 130.02 [C(6'')], 134.48 [C(3'')], 134.57 [C(1''')], 138.13 [br, C(4)], *140.96 [C(8a)], 141.98 [C(1'')], 147.93 [C(6)], 155.09 [C(2''') + C(6''')], 155.18 [C(2)], 157.62 [C(4''')].

*The C(8a) signal was not observed in the ^{13}C NMR spectrum, and the chemical shift was instead determined using clear [^{1}H,^{13}C]-HMBC spectrum correlations with the H(4), H(5) and H(7) signals.

6-(4-(4-(Pyrimidin-5-yl)benzyl)piperidin-1-yl)quinolin-2-amine (116c)



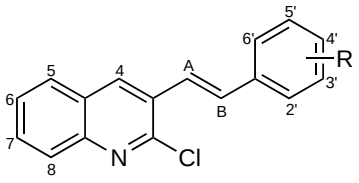
Using General Method 11, **132c** (27 mg, 0.07 mmol) was treated with LiHMDS solution (1.0 M in THF, 143 μL, 0.14 mmol), $Pd(dba)_2$ (0.4 mg, 0.7 μmol) and DavePhos (0.3 mg,

0.8 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **116c** as a brown oil (12 mg, 47%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{25}H_{25}N_5$: 396.2188; found 396.2181. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51 [2H, qd, $^2J_{(3'/5')ax,(3'/5')eq} = {}^3J_{(2'/6')ax,(3'/5')ax} = {}^3J_{(3'/5')ax,4'ax} = 12.0$ Hz, $^3J_{(2'/6')eq,(3'/5')ax} = 3.2$ Hz, H(3'$_{ax}$) + H(5'$_{ax}$)], 1.69-1.89 [3H, m, H(3'$_{eq}$) + H(4'$_{ax}$) + H(5'$_{eq}$)], 2.64-2.76 [4H, m, H(2'$_{ax}$) + H(6'$_{ax}$) + H(A)], 3.70 [2H, br d‡, $^2J_{(2'/6')ax,(2'/6')eq} = 12.0$ Hz, H(2'$_{eq}$) + H(6'$_{eq}$)], 5.08 [2H, br s, NH_2], 6.70 [1H, d, $^3J_{3,4} = 8.8$ Hz, H(3)], 6.97 [1H, d, $^4J_{5,7} = 2.6$ Hz, H(5)], 7.31-7.40 [3H, m, H(7) + H(2") + H(6")], 7.50-7.55 [2H, m, H(3") + H(5")], 7.59 [1H, d, $^3J_{7,8} = 9.2$ Hz, H(8)], 7.79 [1H, d, $^3J_{3,4} = 8.8$ Hz, H(4)], 8.96 [2H, s, H(2'") + H(6'")], 9.20 [1H, s, H(4'")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.23 [C(3') + C(5')], 37.93 [C(4')], 42.94 [C(A)], 50.83 [C(2') + C(6')], 111.41 [C(5)], 112.05 [C(3)], 123.87 [C(7)], 124.11 [C(4a)], 125.63 [C(8)], 127.00 [C(3") + C(5")], 130.40 [C(2") + C(6")], 132.08 [C(4")], 134.33 [C(1'")], 138.16 [C(4)], 140.85 [br, C(8a)], 141.78 [C(1")], 147.96 [C(6)], 154.90 [C(2'") + C(6'")], 155.17 [C(2)], 157.46 [C(4'")].

6.4 2-Aminoquinolines with a 3-position phenethyl-type substituent

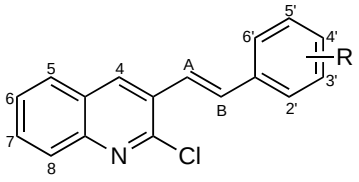
6.4.1 Investigation of synthetic pathway for 3-position extended quinolines

General Method 14: Horner-Emmons reaction for synthesis of 3-position extended 2-chloroquinoline derivatives using sodium hydride



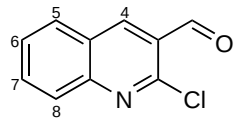
A solution of diethyl benzylphosphonate derivative (1.3 eq) in anhydrous THF was added to a stirring suspension of sodium hydride (60% dispersion in mineral oil, 3 eq) in THF under an atmosphere of nitrogen. The mixture was stirred for 30 min and a solution of quinoline **144** (1 eq) in THF was added dropwise. The mixture was stirred at room temperature for 4 hr or until complete then quenched with water and extracted with ethyl acetate (3 x 30 mL). The organic extracts were washed with water then dried over $MgSO_4$, filtered, and concentrated by evaporation under reduced pressure. The residue was chromatographed over silica gel using the specified eluant.

General Method 15: Horner-Emmons reaction for synthesis of 3-position extended 2-chloroquinoline derivatives using sodium *tert*-butoxide



A solution of diethyl benzylphosphonate derivative (1.4 eq) in anhydrous DMF was added to a suspension of sodium *tert*-butoxide (1.6 eq) in DMF under an atmosphere of nitrogen. The mixture was stirred for 30 min and a solution of quinoline **144** (1 eq) in DMF was added dropwise. The mixture was stirred at room temperature for 4 hr or until complete then quenched with water and extracted with ethyl acetate (x3). The organic extracts were washed with water then dried over $MgSO_4$, filtered, and concentrated by evaporation under reduced pressure. The residue was chromatographed over silica gel using the specified eluant.

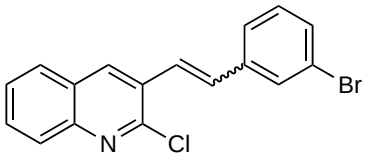
2-Chloroquinoline-3-carbaldehyde (144)



Phosphorous oxychloride (24.1 mL, 258 mmol) was added dropwise to DMF (7.2 mL, 93 mmol) stirred at 0°C. Acetanilide (5.00 g, 37 mmol) was added portionwise, and the mixture was stirred at 0°C until homogeneous then at 80°C overnight. The solution was cooled to 0°C then added slowly to ice water (250 mL). The resultant precipitate was collected by vacuum filtration and recrystallised from ethyl acetate to give **144** as a yellow needle-like crystals (2.99 g, 42%). MP: 151-154°C (lit.[134] 148-149°C). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{10}H_6{}^{35}ClNO/C_{10}H_6{}^{37}ClNO$: 192.0216/194.0187; found 192.0210/194.0183. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 [1H, ddd, $^3J_{5,6} = 8.1$ Hz, $^3J_{6,7} = 7.0$ Hz, $^4J_{6,8} = 1.1$ Hz, H(6)], 7.89 [1H, ddd, $^3J_{7,8} = 8.5$ Hz, $^3J_{6,7} = 7.0$ Hz, $^4J_{5,7} = 1.1$ Hz, H(7)], 8.00 [1H, dd, $^3J_{5,6} = 8.1$ Hz, $^4J_{5,7} = 1.1$ Hz, H(5)], 8.09 [1H, br d‡, $^3J_{7,8} = 8.5$ Hz, H(8)], 8.77 [1H, s, H(4)], 10.57 [1H, s, CHO].

Data was consistent with that reported in literature previously.[77]

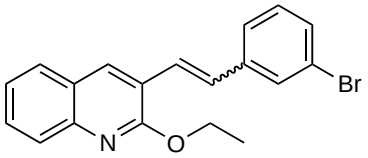
3-(3-Bromostyryl)-2-chloroquinoline (145b)



Synthesis method a. Using General Method 12, **36l** (302 mg, 0.98 mmol) was reacted with NaH (60% dispersion in mineral oil, 94 mg, 2.35 mmol) and **144** (150 mg, 0.78 mmol) in anhydrous THF (10 mL) for 16 hr. Work-up and purification by flash column chromatography on silica gel eluting with 4:1 dichloromethane/hexane gave **151b** as a white solid (100 mg, 36%) and **145b** as a white solid (86 mg, 25%).

A sample of (*E*)-3-(3-bromostyryl)-2-chloroquinoline (*E*-**145b**) was obtained by column chromatography for the purposes of characterisation. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{11}{}^{79}BrClN/C_{17}H_{11}{}^{81}BrClN$: 343.9842/345.9821; found 343.9834/345.9815. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 [1H, d, $^3J_{A,B} = 16.2$ Hz, H(B)], 7.26 [1H, t, $^3J_{4',5'} = {}^3J_{5',6'} = 8.0$ Hz, H(5')], 7.44 [1H, br d‡, $^3J_{4',5'} = 8.0$ Hz, H(4')], 7.49 [1H, br d‡, $^3J_{5',6'} = 8.0$ Hz, H(6')], 7.50 [1H, d, $^3J_{A,B} = 16.2$ Hz, H(A)], 7.56 [1H, t, $^3J_{5,6} = {}^3J_{6,7} = 7.8$ Hz, H(6)], 7.67-7.73 [2H, m, H(7) + H(2')], 7.83 [1H, d, $^3J_{5,6} = 7.8$ Hz, H(5)], 7.99 [1H, d, $^3J_{7,8} = 8.5$ Hz, H(8)], 8.34 [1H, s, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 123.15 [C(3')], 125.09 [C(A)], 125.68 [C(6')], 127.50 [C(6)], 127.54 [C(4a)], 127.72 [C(5)], 128.46 [C(8)], 129.90 [C(3)], 129.91

[C(2')], 130.46 [C(5')], 130.58 [C(7)], 131.48 [C(4')], 131.73 [C(B)], 134.12 [C(4)], 138.79 [C(1')], 147.10 [C(8a)], 150.22 [C(2)].

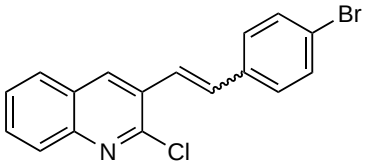


151b

A sample of (*E*)-3-(3-bromostyryl)-2-ethoxyquinoline (*E*-**151b**) was isolated by column chromatography for the purposes of characterisation. MP: 86-88°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{19}H_{16}{}^{79}BrNO/C_{19}H_{16}{}^{81}BrNO$: 354.0494/356.0473; found 354.0488/356.0471. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.52 [3H, t, ^3J = 7.1 Hz, CH_3], 4.63 [2H, q, ^3J = 7.1 Hz, OCH_2], 7.21-7.28 [2H, m, H(B) + H(5')], 7.33-7.42 [3H, m, H(6) + H(A) + H(4')], 7.46 [1H, br d‡, $^3J_{5',6'}$ = 8.0 Hz, H(6')], 7.58 [1H, ddd, $^3J_{7,8}$ = 8.4 Hz, $^3J_{6,7}$ = 7.0 Hz, $^4J_{5,7}$ = 1.4 Hz, H(7)], 7.69-7.74 [2H, m, H(5) + H(2')], 7.80 [1H, br d‡, $^3J_{7,8}$ = 8.4 Hz, H(8)], 8.13 [1H, s, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.80 [CH_3], 62.29 [OCH_2], 122.22 [C(3)], 123.06 [C(3')], 124.34 [C(6)], 124.58 [C(A)], 125.42 [C(4a)], 125.52 [C(6')], 127.04 [C(8)], 127.58 [C(5)], 129.51 [C(7)], 129.64 [C(2')], 130.06 [C(B)], 130.32 [C(5')], 130.79 [C(4')], 134.42 [C(4)], 139.84 [C(1')], 146.12 [C(8a)], 159.72 [C(2)].

Synthesis method b. Using General Method 12, **36l** (192 mg, 0.63 mmol) was reacted with NaH (60% dispersion in mineral oil, 42 mg, 1.0 mmol) and **144** (100 mg, 0.52 mmol) in anhydrous THF (10 mL) for 1 hr. Work-up and purification by flash column chromatography on silica gel eluting with 4:1 dichloromethane/hexane gave **145b** as a white solid (86 mg, 34%). Data as above.

3-(4-Bromostyryl)-2-chloroquinoline (145c)

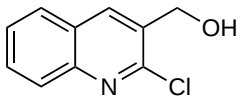


Synthesis method a. Using General Method 12, **36m** (0.48 g, 1.5 mmol) was reacted with NaH (60% dispersion in mineral oil, 0.12 g, 3.0 mmol) and **144** (250 mg, 1.3 mmol) in anhydrous THF (10 mL) for 1 hr. Work-up and purification by flash column chromatography on silica gel eluting with 4:1 dichloromethane/hexane gave **145c** as a white solid (111 mg, 25%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{11}{}^{79}BrClN/C_{17}H_{11}{}^{81}BrClN$: 343.9842/345.9821; found 343.9834/345.9814. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.77 and 6.77 [0.2H, *AB*, *A*:d, *B*:d, $^3J_{*A,*B}(J_{AB})$ = 12.6 Hz, *H(A) + *H(B)], 7.03-7.08 [0.2H, m, *H(2') + *H(6')], 7.10 [0.9H, d, $^3J_{A,B}$ = 16.2 Hz, H(B)], 7.29-7.33 [0.2H, m, *H(3') + *H(5')], 7.40-7.46 [1.8H, m, H(2')

+ H(6')], 7.46-7.60 [3.8H, m, H(A) + H(6) + H(3') + H(5') + *H(5) + *H(6)], 7.66-7.73 [1H, m, H(7) + *H(7)], 7.82 [0.9H, br d‡, $^3J_{5,6}$ = 8.1 Hz, H(5)], 7.92 [0.1H, s, *H(4)], 7.96-8.02 [1H, m, H(8) + *H(8)], 8.34 [0.9H, s, H(4)].

*Denotes signals corresponding to *Z*-isomer.

A crude mixture of recovered **36m** and (2-chloroquinolin-3-yl)methanol (**152**) was also obtained.



152

Synthesis method b. LiHMDS solution (1M in THF, 2.6 mL, 2.6 mmol) was added dropwise to a solution of **36m** (750 mg, 2.4 mmol) in THF stirred under an atmosphere of nitrogen, and mixture was stirred for 10 min. A solution of **144** (389 mg, 2.0 mmol) in THF (3 mL) was added dropwise, and the mixture was stirred at room temperature for 1 hr then quenched with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The organic extracts were dried over $MgSO_4$, filtered, and volatile solvent removed by evaporation under reduced pressure to give a mixture containing recovered **36m** and **152**. The desired product **145c** was not observed.

Synthesis method c. Using General Method 12, **36m** (0.48 g, 1.5 mmol) was reacted with sodium *tert*-butoxide (176 mg, 1.8 mmol) and **144** (250 mg, 1.3 mmol) in anhydrous THF (10 mL) for 1 hr. Work-up and purification by flash column chromatography on silica gel eluting with 4:1 dichloromethane/hexane gave **145c** as a white solid (160 mg, 36%). Data as above.

A crude mixture of recovered **36m** and (2-chloroquinolin-3-yl)methanol (**152**) was also obtained.

Synthesis method d. Using General Method 12, **36m** (0.48 g, 1.5 mmol) was reacted with NaH (60% dispersion in mineral oil, 88 mg, 2.2 mmol) and **144** (250 mg, 1.3 mmol) in anhydrous DMF (10 mL) for 1 hr. Work-up and purification by flash column chromatography on silica gel eluting with 4:1 dichloromethane/hexane gave **145c** as a white solid (347 mg, 77%). Data as above.

Synthesis method e. LiHMDS solution (1M in THF, 940 μL, 0.94 mmol) was added dropwise to a solution of **36m** (192 mg, 0.62 mmol) in DMF (6 mL) stirred under an atmosphere of nitrogen, and mixture was stirred for 10 min. A solution of **144** (100 mg, 0.52 mmol) in DMF (3 mL) was added dropwise, and the mixture was stirred at room temperature for 1 hr then quenched with water (30 mL) and extracted with ethyl acetate (3 x 40 mL). The

organic extracts were washed with water (2 x 100 mL) dried over $MgSO_4$, filtered, and volatile solvent removed by evaporation under reduced pressure. ^{1}H NMR analysis of the crude mixture indicated low conversion to the desired product and a large amount of **152** was present, and further purification was not attempted.

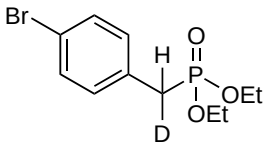
Synthesis method f. Using General Method 15, **36m** (192 mg, 0.62 mmol), **144** (100 mg, 0.52 mmol), and sodium *tert*-butoxide (90 mg, 0.94 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed by column chromatography eluting with dichloromethane gave **145c** as an off-white solid (141 mg, 78%). $R_f = 0.20$ (1:1 ethyl acetate/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{17}H_{11}{}^{79}BrClN/C_{17}H_{11}{}^{81}BrClN$: 343.9842/345.9821; found 343.9834/345.9814. Pure samples of each isomer were isolated by chromatography for the purposes of characterisation.

*(*E*)-3-(4-Bromostyryl)-2-chloroquinoline (*E-***145c***):* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 [1H, d, $^3J_{A,B} = 16.2$ Hz, H(B)], 7.40-7.46 [2H, m, H(2') + H(6')], 7.46-7.60 [4H, m, H(A) + H(6) + H(3') + H(5')], 7.69 [1H, ddd, $^3J_{7,8} = 8.4$ Hz, $^3J_{6,7} = 7.2$ Hz, $^4J_{5,7} = 1.2$ Hz, H(7)], 7.82 [1H, br d‡, $^3J_{5,6} = 8.1$ Hz, H(5)], 7.99 [1H, d, $^3J_{7,8} = 8.4$ Hz, H(8)], 8.34 [1H, s, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 122.61 [C(4')], 124.34 [C(A)], 127.48 [C(6)], 127.59 [C(4a)], 127.68 [C(5)], 128.48 [C(8)], 128.54 [C(2') + C(6')], 130.08 [C(3)], 130.49 [C(7)], 132.05 [C(B)], 132.13 [C(3') + C(5')], 133.94 [C(4)], 135.62 [C(1')], 147.05 [C(8a)], 150.21 [C(2)].

*(*Z*)-3-(4-Bromostyryl)-2-chloroquinoline (*Z-***145c***):* ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.77 and 6.77 [2H, *AB*, *A*:d, *B*:d, $^3J_{A,B}(J_{AB}) = 12.6$ Hz, H(A) + H(B)], 7.03-7.08 [2H, m, H(2') + H(6')], 7.29-7.33 [2H, m, H(3') + H(5')], 7.49 [1H, ddd, $^3J_{5,6} = 8.1$ Hz, $^3J_{6,7} = 6.9$ Hz, $^4J_{6,8} = 1.1$ Hz, H(6)], 7.59 [1H, dd, $^3J_{5,6} = 8.1$ Hz, $^4J_{5,7} = 1.4$ Hz, H(5)], 7.70 [1H, ddd, $^3J_{7,8} = 8.3$ Hz, $^3J_{6,7} = 6.9$ Hz, $^4J_{5,7} = 1.4$ Hz, H(7)], 7.92 [1H, s, H(4)], 8.01 [1H, br d‡, $^3J_{7,8} = 8.3$ Hz, H(8)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 121.83 [C(4')], 126.33 [C(A)], 127.06 [C(4a)], 127.30 [C(6)], 127.67 [C(5)], 128.42 [C(8)], 129.76 [C(3)], 130.59 [C(2') + C(6')], 130.66 [C(7)], 131.83 [C(3') + C(5')], 132.24 [C(B)], 134.83 [C(1')], 138.45 [C(4)], 147.10 [C(8a)], 150.53 [C(2)].

Further investigation into reactivity of 2-chloroquinoline-3-carbaldehyde (144)

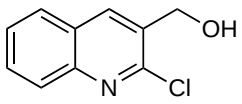
Synthesis method a. LiHMDS solution (1M in THF, 600 μL, 0.6 mmol) was added dropwise to a solution of **36m** (144 mg, 0.47 mmol) in THF stirred under an atmosphere of nitrogen, and mixture was stirred for 10 min. The mixture was quenched with D_2O (1 mL) and the mixture was concentrated to dryness under reduced pressure. ^{1}H NMR analysis of the crude mixture identified signals corresponding to **36m** and **185m**. Integration of the HP doublet signals indicated a 1:5 ratio of the phosphonate compounds, favouring **185m**.



185m

Synthesis method b. A solution of **144** (10 mg, 0.05 mmol) in anhydrous THF was added to anhydrous THF stirring under an atmosphere of nitrogen. The solution was stirred for 1 hr, and then water (1 mL) was added. The mixture was concentrated to dryness by evaporation under reduced pressure, to give recovered **144**.

Synthesis method c. LiHMDS solution (1M in THF, 140 μL, 0.14 mmol) was added dropwise to anhydrous THF (4 mL) stirring under an atmosphere of nitrogen, and then stirred for 10 min. A solution of **144** (15 mg, 0.08 mmol) in anhydrous THF was added dropwise, and the mixture was stirred for 1 hr. The mixture was quenched with water (4 mL) and the mixture was concentrated to dryness under reduced pressure. ^{1}H NMR analysis identified the crude mixture contained mostly **152**, and the presence of the reagent **144** was not observed.



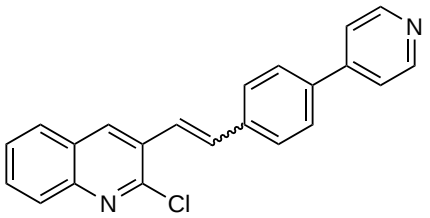
152

(2-Chloroquinolin-3-yl)methanol (**152**): HRMS (ESI+) $[M+H]^+$ calcd. for $C_{10}H_8{}^{35}ClNO$/ $C_{10}H_8{}^{37}ClNO$: 194.0373/196.0343; found 194.0369/196.0342. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.93 [2H, s, OCH_2], 7.57 [1H, ddd, $^{3}J_{5,6} = 8.3$ Hz, $^{3}J_{6,7} = 7.0$ Hz, $^{4}J_{6,8} = 1.0$ Hz, H(6)], 7.72 [1H, ddd, $^{3}J_{7,8} = 8.4$ Hz, $^{3}J_{6,7} = 7.0$ Hz, $^{4}J_{5,7} = 1.3$ Hz, H(7)], 7.84 [1H, br d‡, $^{3}J_{5,6} =$ 8.3 Hz, H(5)], 8.02 [1H, br d‡, $^{3}J_{7,8} = 8.4$ Hz, H(8)], 8.30 [1H, s, H(4)].

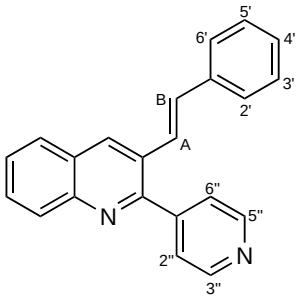
This data is consistent with that reported previously.[135]

Synthesis method d. A solution of **144** (15 mg, 0.08 mmol) in anhydrous THF was added dropwise to a stirring suspension of NaH (60% in mineral oil, 10 mg, 0.25 mmol) in THF under an atmosphere of nitrogen. The mixture was stirred for 1 hr then quenched with water (4 mL) and extracted with dichloromethane (3 x 20 mL). The organic extracts were dried over $MgSO_4$, filtered, and the volatile solvent removed by evaporation under reduced pressure. ^{1}H NMR analysis identified the crude mixture contained mostly **152**, and a small amount of reagent **144** was also present.

2-Chloro-3-(4-(pyridin-4-yl)styryl)quinoline (147c)



Synthesis method a. A mixture of **145c** (110 mg, 0.32 mmol), 4-pyridinylboronic acid (39 mg, 0.32 mmol), $Pd(OAc)_2$ (2.1 mg, 9 μmol), PPh_3 (4.2 mg, 16 μmol), and K_2CO_3 (88 mg, 0.64 mmol) were combined in a glass pressure tube with toluene/ethanol (1:1, 3 mL). The tube was sealed and heated to 100°C for 16 hr, then cooled to room temperature and filtered through Celite®, washing with methanol. The solvent was removed by evaporation under reduced pressure to give a complex crude mixture of products which could not be purified. Column chromatography on silica gel eluting with methanol in dichloromethane (0-5%) yielded a small sample of the major product (*E*)-2-(pyridin-4-yl)-3-styrylquinoline (*E*-**154c**) as a yellow oil (15 mg, 15%).

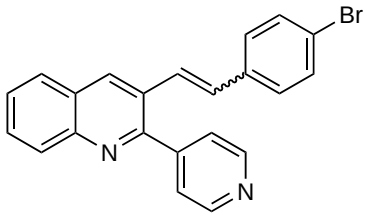


154c

*(*E*)-2-(Pyridin-4-yl)-3-styrylquinoline (*E-***154c***):* $R_f = 0.01$ (dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{13}H_{19}N$: 309.1392; found 309.1386. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 [1H, d, $^3J_{A,B} = 16.1$ Hz, H(A)], 7.21 [1H, d, $^3J_{A,B} = 16.1$ Hz, H(B)], 7.28-7.33 [1H, m, H(4')], 7.34-7.40 [H(3') + H(5')], 7.42-7.47 [2H, m, H(2') + H(6')], 7.60 [1H, ddd, $^3J_{5,6} = 8.1$ Hz, $^3J_{6,7} = 6.9$ Hz, $^4J_{6,8} = 1.1$ Hz, H(6)], 7.64-7.68 [2H, m, H(2") + H(6")], 7.74 [1H, ddd, $^3J_{7,8} = 8.4$ Hz, $^3J_{6,7} = 6.9$ Hz, $^4J_{5,7} = 1.0$ Hz, H(7)], 7.91 [1H, br dd‡, $^3J_{5,6} = 8.1$ Hz, $^4J_{5,7} = 1.0$ Hz, H(5)], 8.14 [1H, br d‡, $^3J_{7,8} = 8.4$ Hz, H(8)], 8.47 [1H, s, H(4)], 8.75-8.81 [2H, m, H(3") + H(5")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 124.53 [C(2") + C(6")], 125.44 [C(A)], 126.90 [C(2') + C(6')], 127.60 [C(6)], 127.72 [C(5)], 127.99 [C(4a)], 128.51 [C(4')], 129.02 [C(3') + C(5')], 129.67 [C(8)], 129.91 [C(3)], 130.05 [C(7)], 132.42 [C(B)], 133.50 [C(4)], 136.84 [C(1')], 147.49 [C(8a)], 147.83 [C(1")], 150.10 [C(3") + C(5")], 156.21 [C(2)].

HRMS analysis of the crude product mixture identified masses corresponding to other products which could not be isolated; potential products reported below.

*2-Chloro-3-(4-(pyridin-4-yl)styryl)quinoline (**147c**):* HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{15}{}^{35}ClN_2/C_{22}H_{15}{}^{37}ClN_2$: 343.1002/345.0973; found 343.0998/345.0985.



155c

*3-(4-Bromostyryl)-2-(pyridin-4-yl)quinoline (**155c**):* HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{15}{}^{79}BrN_2/C_{22}H_{15}{}^{81}BrN_2$: 387.0497/389.0476; found 387.0517/389.0474.

Synthesis method b.[95] A mixture of **145c** (80 mg, 0.23 mmol), 4-pyridinylboronic acid (29 mg, 0.24 mmol), $Pd(OAc)_2$ (1.6 mg, 7 μmol), PPh_3 (3.0 mg, 11 μmol), and K_2CO_3 (64 mg, 0.46 mmol) were combined in a glass pressure tube with toluene (3 mL). The tube was sealed and heated to 80°C for 16 hr, then cooled to room temperature and filtered through Celite®, washing with methanol. The solvent was removed by evaporation under reduced pressure to give a complex crude mixture of products which could not be purified.

Synthesis method c.[96] A mixture of **145c** (41 mg, 0.12 mmol), 4-pyridinylboronic acid (15 mg, 0.12 mmol), $Pd(OAc)_2$ (0.8 mg, 3.6 μmol), $P(o\text{-tol})_3$ (1.8 mg, 5.9 μmol), and Na_2CO_3 (50 mg, 0.47 mmol) were combined in a glass pressure tube with 1,4-dioxane (3 mL). The tube was sealed and heated to 55°C for 16 hr, then cooled to room temperature and filtered through Celite®, washing with methanol. The solvent was removed by evaporation under reduced pressure to give a complex crude mixture of products which could not be purified. HRMS did not identify peaks consistent with the desired product.

Synthesis method d.[96] A mixture of **145c** (41 mg, 0.12 mmol), 4-pyridinylboronic acid (15 mg, 0.12 mmol), $Pd(OAc)_2$ (0.8 mg, 3.6 μmol), $P(o\text{-tol})_3$ (1.8 mg, 5.9 μmol), and Na_2CO_3 (50 mg, 0.47 mmol) were combined in 1,4-dioxane (3 mL) and heated at reflux for 16 hr. The mixture was cooled to room temperature and filtered through Celite®, washing with methanol. The solvent was removed by evaporation under reduced pressure to give a complex crude mixture of products which could not be purified. HRMS did not identify peaks consistent with the desired product.

Synthesis method e. LiHMDS solution (1M in THF, 881 μL, 0.88 mmol) was added dropwise to a solution of **157c** (148 mg, 0.48 mmol) in THF stirred under an atmosphere of nitrogen, and mixture was stirred for 10 min. A solution of **144** (84 mg, 0.44 mmol) in THF (3 mL) was added dropwise, and the mixture was stirred at room temperature for 1 hr then quenched with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The organic extracts were dried over $MgSO_4$, filtered, and volatile solvent removed by evaporation under reduced pressure.

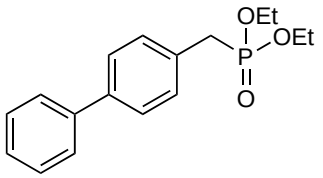
The residue was chromatographed over silica gel eluting with dichloromethane, to give a crude mixture containing predominantly **152** and a small amount of the desired product **147c**.

Synthesis method f. Using General Method 15, **157c** (263 mg, 0.86 mmol), **144** (118 mg, 0.62 mmol), and sodium *tert*-butoxide (142 mg, 1.48 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed by column chromatography eluting with dichloromethane gave **147c** as a yellow solid (211 mg, 100%). $R_f = 0.12$ (2.5% methanol in dichloromethane). MP: degraded 137°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{15}{}^{35}ClN_2/C_{22}H_{15}{}^{37}ClN_2$: 343.1002/345.0973; found 343.0999/345.0979. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81 [0.15H, d, $^3J_{*A,*B} = 12.1$ Hz, *H(A)], 6.89 [0.15H, d, $^3J_{*A,*B} = 12.1$ Hz, *H(B)], 7.23 [0.85H, d, $^3J_{A,B} = 16.2$ Hz, H(B)], 7.28-7.32 [0.3H, m, *H(2') + *H(6')], 7.41-7.45 [0.3H, m, *H(2") + *H(6")], 7.45-7.63 [3.85H, m, H(A) + H(6) + H(2") + H(6") + *H(6) + *H(3') + *H(5')], 7.65-7.74 [4.55H, m, H(7) + H(2') + H(3') + H(5') + H(6') + *H(5) + *H(7)], 7.85 [0.85H, d, $^3J_{5,6} = 8.1$ Hz, H(5)], 7.97-8.05 [1.15H, m, H(8) + *H(4) + *H(8)], 8.39 [0.85H, s, H(4)], 8.58-8.64 [0.3H, m, *H(3") + *H(5")], 8.65-8.71 [1.7H, m, H(3") + H(5")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 121.35 [*C(2") + *C(6")], 121.43 [C(2") + C(6")], 124.67 [C(A)], 126.51 [*C(A)], 127.07 [*C(5)], 127.11 [*C(3') + *C(5')], 127.24 [*C(6)], 127.49 [C(6)], 127.52 [C(3') + C(5')], 127.60 [*C(4a)], 127.61 [C(4a)], 127.69 [C(5)], 127.80 [C(2') + C(6')], 128.41 [*C(8)], 128.47 [C(8)], 129.76 [*C(2') + *C(6')], 129.98 [*C(3)], 130.12 [C(3)], 130.51 [C(7)], 130.60 [*C(7)], 132.34 [C(B)], 132.60 [*C(B)], 133.97 [C(4)], 136.83 [*C(1') + *C(4')], 137.28 [*C(1') + *C(4')], 137.52 [C(1')], 138.10 [C(4')], 138.49 [*C(4)], 147.06 [C(8a)], 147.09 [*C(8a)], 147.50 [*C(1")], 147.59 [C(1")], 150.26 [C(2)], 150.41 [*C(3") + *C(5")], 150.48 [C(3") + C(5")], 150.57 [*C(2)].

* denotes signals corresponding to *Z*-isomer

A sample of pure (*E*)-2-chloro-3-(4-(pyridin-4-yl)styryl)quinoline (*E*-**147c**) was isolated by column chromatography for the purposes of characterisation. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 [1H, d, $^3J_{A,B} = 16.2$ Hz, H(B)], 7.51-7.64 [4H, m, H(A) + H(6) + H(2") + H(6")], 7.67-7.74 [5H, m, H(7) + H(2') + H(3') + H(5') + H(6')], 7.86 [1H, br d‡, $^3J_{5,6} = 8.1$ Hz, H(5)], 8.00 [1H, br d‡, $^3J_{7,8} = 8.5$ Hz, H(8)], 8.41 [1H, s, H(4)], 8.65-8.72 [2H, m, H(3") + H(5")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 121.48 [br, C(2") + C(6")], 124.73 [C(A)], 127.52 [C(6)], 127.57 [C(3') + C(5')], 127.64 [C(4a)], 127.71 [C(5)], 127.83 [C(2') + C(6')], 128.52 [C(8)], 130.18 [C(3)], 130.54 [C(7)], 132.38 [C(B)], 134.01 [C(4)], 137.55 [C(1')], 138.17 [C(4')], 147.11 [C(8a)], 147.62 [C(1")], 150.31 [C(2)], 150.53 [C(3") + C(5")].

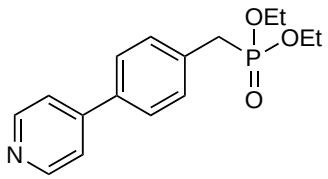
Diethyl ((1,1'-biphenyl)-4-ylmethyl)phosphonate (156c)



Using General Method 13, **36m** (320 mg, 1.0 mmol), phenylboronic acid (152 mg, 1.25 mmol), $Pd(OAc)_2$ (7.0 mg, 31 μmol), PPh_3 (13.7 mg, 52 μmol) and K_2CO_3 (288 mg, 2.1 mmol) in toluene/ethanol (1:1, 4 mL) were reacted for 16 hr. Work-up followed by column chromatography eluting with 2% methanol in dichloromethane gave **156c** as a pale yellow oil (285 mg, 90%). $R_f = 0.16$ (2% methanol in dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 [6H, t, $^3J = 7.1$ Hz, 2 x CH_3], 3.19 [2H, d, $^2J_{H,P} = 21.7$ Hz, PCH_2], 3.97-4.11 [4H, m, 2 x OCH_2], 7.33 [1H, tt, $^3J_{3',4'} = {}^3J_{4',5'} = 7.4$ Hz, $^4J_{2',4'} = {}^4J_{4,6'} = 1.1$ Hz, H(4')], 7.35-7.39 [2H, m, H(2) + H(6)], 7.40-7.46 [2H, m, H(3') + H(5')], 7.52-7.56 [2H, m, H(2') + H(6')], 7.56-7.60 [2H, m, H(3) + H(5)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.50 [d, $^3J_{C,P} = 6.0$ Hz, 2 x CH_3], 33.57 [d, $^1J_{C,P} = 138.2$ Hz, PCH_2], 62.27 [d, $^2J_{C,P} = 6.7$ Hz, 2 x OCH_2], 127.10 [d, $^7J_{C,P} = 0.8$ Hz, C(2') + C(6')], 127.33 [br s, C(4')], 127.36 [d, $^4J_{C,P} = 1.4$ Hz, C(3) + C(5)], 128.86 [C(3') + C(5')], 130.27 [d, $^3J_{C,P} = 6.6$ Hz, C(2) + C(6)], 130.79 [d, $^2J_{C,P} = 9.1$ Hz, C(1)], 139.87 [d, $^5J_{C,P} = 3.9$ Hz, C(4)], 140.83 [d, $^6J_{C,P} = 1.5$ Hz, C(1')].

This data is consistent with that reported previously.[105]

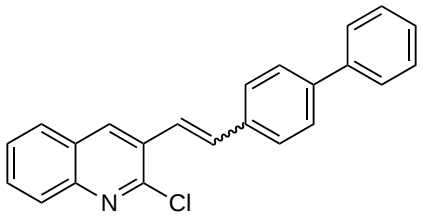
Diethyl 4-(pyridin-4-yl)benzylphosphonate (157c)



Using General Method 13, **36m** (320 mg, 1.04 mmol), 4-pyridinylboronic acid (154 mg, 1.25 mmol), $Pd(OAc)_2$ (7.0 mg, 31 μmol), PPh_3 (13.7 mg, 52 μmol) and K_2CO_3 (288 mg, 2.08 mmol) in 1:1 toluene/ethanol (3 mL) were reacted for 16 hr. Work-up followed by column chromatography eluting with 3% methanol in dichloromethane gave **157c** as a clear oil (307 mg, 97%). $R_f = 0.20$ (1:19 methanol/dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 [6H, t, $^3J = 7.1$ Hz, 2 x CH_3], 3.21 [2H, d, $^2J_{H,P} = 21.8$ Hz, PCH_2], 3.99-4.12 [4H, m, 2 x OCH_2], 7.39-7.46 [2H, m, H(2) + H(6)], 7.47-7.53 [2H, m, H(2') + H(6')], 7.58-7.64 [2H, m, H(3) + H(5)], 8.60-8.70 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.50 [d, $^3J_{C,P} = 6.0$ Hz, 2 x CH_3], 33.66 [d, $^1J_{C,P} = 138.1$ Hz, PCH_2], 62.33 [d, $^2J_{C,P} = 6.7$ Hz, 2 x OCH_2], 121.56 [br s, C(2') + C(6')], 127.21 [d, $^4J_{C,P} = 3.3$ Hz, C(3) + C(5)],

130.63 [d, $^{3}J_{C,P}$ = 6.5 Hz, C(3) + C(5)], 133.00 [d, $^{2}J_{C,P}$ = 9.4 Hz, C(1)], 136.76 [d, $^{5}J_{C,P}$ = 3.8 Hz, C(4)], 147.94 [d, $^{6}J_{C,P}$ = 1.5 Hz, C(1')], 150.35 [C(3') + C(5')].

3-(2-((1,1'-Biphenyl)-4-yl)vinyl)-2-chloroquinoline (146c)



Using General Method 15, **156c** (250 mg, 0.82 mmol), **144** (112 mg, 0.58 mmol), and sodium *tert*-butoxide (135 mg, 1.4 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed by column chromatography eluting with dichloromethane gave **146c** as an off-white solid (156 mg, 78%). HRMS (ESI+) $[M+H]^{+}$ calcd. for $C_{23}H_{16}{}^{35}ClN/C_{23}H_{16}{}^{37}ClN$: 342.1050/344.1020; found 342.1045/344.1021. ^{1}H NMR (500 MHz, $CDCl_3$): 6.75 [0.3H, d, $^{3}J_{A,B}$ = 12.1 Hz, *H(A) or *H(B)], 6.88 [0.3H, d, $^{3}J_{A,B}$ = 12.1 Hz, *H(A) or *H(B)], 7.17-7.73 [12.7H, m, H(6) + H(7) + H(A) + H(B) + Ph + *H(5) + *H(6) + *H(7) + *Ph], 7.84 [0.7H, d, $^{3}J_{5,6}$ = 8.0 Hz, H(5)], 7.97-8.05 [1.3H, m, H(8) + *H(4) + *H(8)], 8.39 [1H, s, H(4)].

* denotes signals corresponding to *Z*-isomer

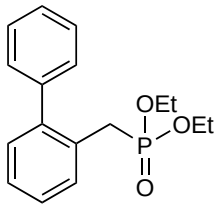
Due to overlap of signals in the product mixture the ^{13}C NMR spectrum could not be unambiguously assigned.

A sample of pure (*E*)-3-(2-((1,1'-biphenyl)-4-yl)vinyl)-2-chloroquinoline (*E*-**146c**)was isolated by column chromatography for the purposes of characterisation. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 [1H, d, $^{3}J_{A,B}$ = 16.3 Hz, H(B)], 7.37 [1H, tt, $^{3}J_{3'',4''} = {}^{3}J_{4'',5''}$ = 7.4 Hz, $^{4}J_{2'',4''} = {}^{4}J_{4'',6''}$ = 1.1 Hz, H(4'')], 7.43-7.49 [2H, m, H(3'') + H(5'')], 7.53-7.60 [2H, m, H(A) + H(6)], 7.61-7.72 [7H, m, H(7) + H(2') + H(3') + H(5') + H(6') + H(2'') + H(6'')], 7.85 [1H, br d‡, $^{3}J_{5,6}$ = 8.0 Hz, H(5)], 8.00 [1H, br d‡, $^{3}J_{7,8}$ = 8.5 Hz, H(8)], 8.39 [1H, s, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 123.64 [C(A)], 127.11 [C(2'') + C(6'')], 127.43 [C(6)], 127.59 [C(2') + C(6')], 127.65 [C(3') + C(5')], 127.68 [*C(5)], 127.70 [*C(4'')],128.49 [C(8)], 129.01 [C(3'') + C(5'')], 130.35 [C(7)], 130.49 [C(3)], 132.91 [C(B)], 133.79 [C(4)], 135.75 [C(1')], 140.59 [C(1'')], 141.47 C(4')], 146.98 [C(8a)], 150.39 [C(2)].

*Some ^{13}C NMR signals could not be unambiguously assigned due to close proximity of chemical shifts. The C(4a) signal was not observed; 2D HMBC correlations indicated this signal was overlapped with a signal at 127.7 ppm, but due to close proximity of several signals in this range the C(4a) signal could not be unambiguously assigned.

6.4.2 Synthesis of biaryl-extended diethylphosphonate derivatives

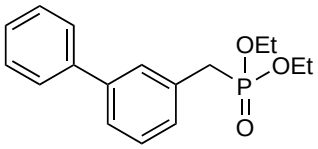
Diethyl ((1,1'-biphenyl)-2-ylmethyl)phosphonate (156a)



Using General Method 13, **36k** (320 mg, 1.0 mmol), phenylboronic acid (152 mg, 1.25 mmol), $Pd(OAc)_2$ (7.0 mg, 31 μmol), PPh_3(13.7 mg, 52 μmol) and K_2CO_3 (288 mg, 2.1 mmol) in toluene/ethanol (1:1, 4 mL) were reacted for 16 hr. Work-up followed by column chromatography eluting with 2% methanol in DCM gave **156a** as a pale yellow oil (282 mg, 89%). R_f = 0.24 (2.5% methanol in dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 [6H, t, ^3J = 7.1 Hz, 2 x CH_3], 3.18 [2H, d, $^2J_{H,P}$ = 22.2 Hz, PCH_2], 3.87-4.01 [4H, m, 2 x OCH_2], 7.22-7.45 [8H, m, H(3) + H(4) + H(5) + H(2') + H(3') + H(4') + H(5') + H(6')], 7.54-7.60 [1H, m, H(6)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.41 [d, $^3J_{C,P}$ = 6.2 Hz, 2 x CH_3], 30.36 [d, $^1J_{C,P}$ = 138.3 Hz, PCH_2], 62.00 [d, $^2J_{C,P}$ = 6.7 Hz, 2 x OCH_2], 126.88 [d, $^4J_{C,P}$ = 3.5 Hz, *C(3) or C(5)], 127.17 [C(4')], 127.46 [d, $^4J_{C,P}$ = 3.3 Hz, *C(3) or C(5)], 128.28 [C(3') + C(5')], 129.20 [d, $^2J_{C,P}$ = 8.5 Hz, C(1)], 129.62 [d, $^5J_{C,P}$ = 0.7 Hz, C(2') + C(6')], 130.52-130.57 [m, C(4) + C(6)], 141.24 [d, $^4J_{C,P}$ = 0.9 Hz, C(1')], 142.70 [d, $^3J_{C,P}$ = 8.4 Hz, C(2)].

*Interpretation of spectra and 2D NMR correlations could not achieve unambiguous assignment of all NMR signals due to overlapped signals in the ^{1}H NMR spectrum.

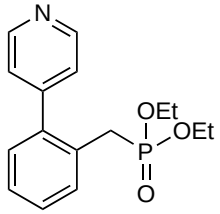
Diethyl ((1,1'-biphenyl)-3-ylmethyl)phosphonate (156b)



Using General Method 12, **36l** (500 mg, 1.6 mmol), phenylboronic acid (240 mg, 2.0 mmol), $Pd(OAc)_2$ (11 mg, 49 μmol), PPh_3 (22 mg, 84 μmol) and K_2CO_3 (340 mg, 2.5 mmol) in toluene (2.5 mL) were reacted for 16 hr. Work-up followed by column chromatography eluting with 3% methanol in DCM gave **156b** as a pale yellow oil (431 mg, 87%). R_f = 0.21 (2.5% methanol in dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 [6H, t, ^3J = 7.1 Hz, 2 x CH_3], 3.22 [2H, d, $^2J_{H,P}$ = 21.6 Hz, PCH_2], 3.96-4.11 [4H, m, 2 x OCH_2], 7.29 [1H, br d‡, $^3J_{5,6}$ = 7.6 Hz, H(6)], 7.34 [1H, t, $^3J_{3',4'} = {}^3J_{4',5'}$ = 7.7 Hz, H(4')], 7.38 [1H, t, $^3J_{4,5} = {}^3J_{5,6}$

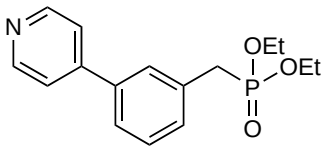
= 7.6 Hz, H(5)], 7.40-7.46 [2H, m, H(3') + H(5')], 7.48 [1H, br d‡, $^{3}J_{4,5}$ = 7.6 Hz, H(4)], 7.53 [1H, br d‡, $^{4}J_{2,P}$ = 1.8 Hz, H(2)], 7.56-7.61 [2H, m, H(2') + H(6')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.53 [d, $^{3}J_{C,P}$ = 5.8 Hz, 2 x CH_3], 34.01 [d, $^{1}J_{C,P}$ = 138.1 Hz, PCH_2], 62.28 [d, $^{2}J_{C,P}$ = 6.7 Hz, 2 x OCH_2], 125.83 [d, $^{5}J_{C,P}$ = 3.5 Hz, C(4)], 127.26 [C(2') + C(6')], 127.49 [C(4')], 128.75 [d, $^{3}J_{C,P}$ = 6.8 Hz, C(2)], 128.78 [d, $^{3}J_{C,P}$ = 6.4 Hz, C(6)], 128.87 [C(3') + C(5')], 129.06 [d, $^{4}J_{C,P}$ = 3.2 Hz, C(5)], 132.27 [d, $^{2}J_{C,P}$ = 9.2 Hz, C(1)], 140.97 [C(1')], 141.56 [d, $^{4}J_{C,P}$ = 3.3 Hz, C(3)].

Diethyl 2-(pyridin-4-yl)benzylphosphonate (157a)



Using General Method 13, **36k** (320 mg, 1.04 mmol), 4-pyridinylboronic acid (154 mg, 1.25 mmol), $Pd(OAc)_2$ (7.0 mg, 31 μmol), PPh_3 (13.7 mg, 52 μmol) and K_2CO_3 (288 mg, 2.08 mmol) in 1:1 toluene/ethanol (3 mL) were reacted for 16 hr. Work-up followed by column chromatography eluting with 3% methanol in dichloromethane gave **157a** as a pale yellow oil (285 mg, 90%). R_f = 0.20 (3% methanol in dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 [6H, t, ^{3}J = 7.1 Hz, 2 x CH_3], 3.13 [2H, d, $^{2}J_{H,P}$ = 22.3 Hz, PCH_2], 3.91-4.07 [4H, m, 2 x OCH_2], 7.23 [1H, br d‡, $^{3}J_{3,4}$ = 7.6 Hz, H(3)], 7.33 [1H, tt, $^{3}J_{4,5}$ = $^{3}J_{5,6}$ = 7.5 Hz, $^{4}J_{3,5}$ = $^{5}J_{5,P}$ = 1.5 Hz, H(5)], 7.36-7.42 [3H, m, H(4) + H(2') + H(6')], 7.58 [1H, br d‡, $^{3}J_{5,6}$ = 7.5 Hz, H(6)], 8.65-8.70 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.42 [d, $^{3}J_{C,P}$ = 5.9 Hz, 2 x CH_3], 30.48 [d, $^{1}J_{C,P}$ = 138.9 Hz, PCH_2], 62.15 [d, $^{2}J_{C,P}$ = 6.8 Hz, 2 x OCH_2], 124.66 [C(2') + C(6')], 127.24 [d, $^{4}J_{C,P}$ = 3.4 Hz, C(5)], 128.51 [d, $^{5}J_{C,P}$ = 3.5 Hz, C(4)], 128.96 [d, $^{2}J_{C,P}$ = 8.5 Hz, C(1)], 129.97 [d, $^{4}J_{C,P}$ = 2.8 Hz, C(3)], 130.94 [d, $^{3}J_{C,P}$ = 4.8 Hz, C(6)], 139.94 [d, $^{3}J_{C,P}$ = 7.9 Hz, C(2)], 149.08 [d, $^{4}J_{C,P}$ = 1.6 Hz, C(1')], 149.82 [C(3') + C(5')].

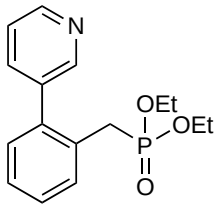
Diethyl 3-(pyridin-4-yl)benzylphosphonate (157b)



Using General Method 13, **36l** (320 mg, 1.04 mmol), 4-pyridinylboronic acid (154 mg, 1.25 mmol), $Pd(OAc)_2$ (7.0 mg, 31 μmol), PPh_3 (13.7 mg, 52 μmol) and K_2CO_3 (288 mg, 2.08 mmol) in 1:1 toluene/ethanol (3 mL) were reacted for 16 hr. Work-up followed by column

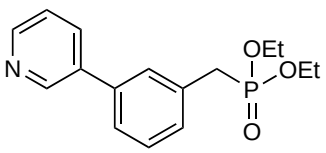
chromatography eluting with 2% methanol in dichloromethane gave **157b** as a pale yellow oil (258 mg, 81%). R_f = 0.18 (1:19 methanol/dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 [6H, t, ^3J = 7.1 Hz, 2 x CH_3], 3.23 [2H, d, $^2J_{H,P}$ = 21.7 Hz, PCH_2], 3.97-4.13 [4H, m, 2 x OCH_2], 7.38 [1H, br d‡, $^3J_{5,6}$ = 7.6 Hz, H(6)], 7.44 [1H, t, $^3J_{4,5}$ = $^3J_{5,6}$ = 7.6 Hz, H(5)], 7.49-7.55 [3H, m, H(4) + H(2') + H(6')], 7.59 [2H, br q‡, $^4J_{H,P}$ = $^4J_{2,4}$ = $^4J_{2,6}$ = 1.9 Hz, H(2)], 8.63-8.68 [2H, m, H(3') + H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.52 [d, $^3J_{C,P}$ = 6.1 Hz, 2 x CH_3], 33.92 [d, $^1J_{C,P}$ = 138.5 Hz, PCH_2], 62.34 [d, $^2J_{C,P}$ = 6.8 Hz, 2 x OCH_2], 121.75 [C(2') + C(6')], 125.68 [d, $^5J_{C,P}$ = 3.6 Hz, C(4)], 128.55 [d, $^3J_{C,P}$ = 6.6 Hz, C(2)], 129.42 [d, $^4J_{C,P}$ = 3.1 Hz, C(5)], 130.57 [d, $^3J_{C,P}$ = 6.6 Hz, C(6)], 132.89 [d, $^1J_{C,P}$ = 8.8 Hz, C(1)], 138.53 [d, $^4J_{C,P}$ = 2.9 Hz, C(3)], 148.12 [C(1')], 150.36 [C(3') + C(5')].

Diethyl 2-(pyridin-3-yl)benzylphosphonate (158a)



Using General Method 13, **36k** (320 mg, 1.04 mmol), 3-pyridinylboronic acid (154 mg, 1.25 mmol), $Pd(OAc)_2$ (7.0 mg, 31 μmol), PPh_3 (13.7 mg, 52 μmol) and K_2CO_3 (288 mg, 2.08 mmol) in 1:1 toluene/ethanol (3 mL) were reacted for 16 hr. Work-up followed by column chromatography eluting with 3% methanol in DCM gave **158a** as a yellow oil (305 mg, 96%). R_f = 0.12 (1:19 methanol/dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 [6H, t, ^3J = 7.1 Hz, 2 x CH_3], 3.12 [2H, d, $^2J_{H,P}$ = 22.3 Hz, PCH_2], 3.88-4.06 [4H, m, 2 x OCH_2], 7.24 [1H, br d‡, $^3J_{3,4}$ = 7.6 Hz, H(3)], 7.30-7.41 [3H, m, H(4) + H(5) + H(5')], 7.58 [1H, br ddd‡, $^3J_{5,6}$ = 7.6 Hz, $^4J_{H,P}$ = 2.4 Hz, $^4J_{4,6}$ = 1.4 Hz, H(6)], 7.82 [1H, dt, $^3J_{5',6'}$ = 7.8 Hz, $^4J_{2',6'}$ = $^4J_{4',6'}$ = 2.0 Hz, H(6')], 8.60-8.64 [2H, m, H(2') + H(4')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.45 [d, $^3J_{C,P}$ = 6.0 Hz, 2 x CH_3], 30.61 [d, $^1J_{C,P}$ = 138.8 Hz, PCH_2], 62.17 [d, $^2J_{C,P}$ = 6.7 Hz, 2 x OCH_2], 123.11 [C(5')], 127.23 [d, $^5J_{C,P}$ = 3.6 Hz, C(4)], 128.34 [d, $^4J_{C,P}$ = 3.4 Hz, C(5)], 129.68 [C(1)], 130.66 [d, $^4J_{C,P}$ = 2.9 Hz, C(3)], 130.93 [d, $^3J_{C,P}$ = 5.0 Hz, C(6)], 136.89 [d, $^4J_{C,P}$ = 1.0 Hz, C(1')], 137.09 [d, $^5J_{C,P}$ = 0.8 Hz, C(6')], 138.95 [d, $^2J_{C,P}$ = 8.4 Hz, C(2)], 148.60 [C(4')], 150.28 [d, $^5J_{C,P}$ = 1.0 Hz, C(2')].

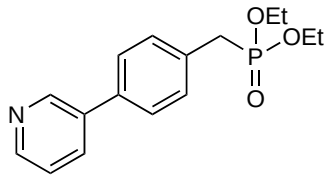
Diethyl 3-(pyridin-3-yl)benzylphosphonate (158b)



Using General Method 13, **36l** (300 mg, 0.98 mmol), 3-pyridinylboronic acid (180 mg, 1.5

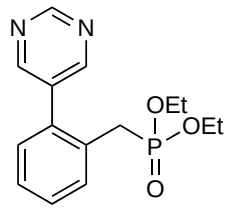
mmol), $Pd(OAc)_2$ (6.6 mg, 29 μmol), PPh_3 (13 mg, 50 μmol) and K_2CO_3 (270 mg, 2.0 mmol) in 1:1 toluene/ethanol (3 mL) were reacted for 16 hr. Work-up followed by column chromatography eluting with 2% methanol in dichloromethane gave **158b** as a pale yellow oil (204 mg, 68%). $R_f = 0.28$ (5% methanol in dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 [6H, t, $^3J = 7.1$ Hz, 2 x CH_3], 3.23 [2H, d, $^2J_{H,P} = 21.7$ Hz, PCH_2], 4.00-4.12 [4H, m, 2 x OCH_2], 7.33-7.38 [2H, m, H(6) + H(5')], 7.43 [1H, t, $^3J_{4,5} = {}^3J_{5,6} = 7.6$ Hz, H(5)], 7.48 [1H, dq, $^3J_{4,5} = 7.6$ Hz, $^4J_{2,4} = {}^4J_{4,6} = {}^6J_{4,P} = 1.5$ Hz, H(4)], 7.53 [1H, q, $^4J_{2,4} = {}^4J_{2,6} = {}^4J_{2,P} = 1.5$ Hz, H(2)], 7.87 [1H, ddd, $^3J_{5',6'} = 7.9$ Hz, $^4J_{2'/6'} = 2.0$ Hz, $^4J_{4'/6'} = 1.6$ Hz, H(6')], 8.59 [1H, dd, $^3J_{4',5'} = 4.8$ Hz, $^4J_{4',6'} = 1.6$ Hz, H(4')], 8.84 [1H, d, $^4J_{2',6'} = 2.0$ Hz, H(2')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.50 [d, $^3J_{C,P} = 5.8$ Hz, 2 x CH_3], 33.91 [d, $^1J_{C,P} = 138.2$ Hz, PCH_2], 62.26 [d, $^2J_{C,P} = 6.8$ Hz, 2 x OCH_2], 123.61 [C(5')], 125.79 [d, $^5J_{C,P} = 3.5$ Hz, C(4)], 128.65 [d, $^3J_{C,P} = 6.7$ Hz, C(2)], 129.35 [d, $^4J_{C,P} = 2.9$ Hz, C(5)], 129.59 [d, $^3J_{C,P} = 6.5$ Hz, C(6)], 132.77 [d, $^2J_{C,P} = 9.2$ Hz, C(1)], 134.44 [C(6')], 136.38 [C(1')], 138.19 [d, $^4J_{C,P} = 2.9$ Hz, C(3)], 148.39 [C(2')], 148.69 [C(4')].

Diethyl 4-(pyridin-3-yl)benzylphosphonate (158c)



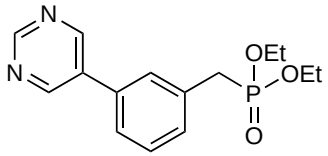
Using General Method 13, **36m** (300 mg, 0.98 mmol), 3-pyridinylboronic acid (180 mg, 1.46 mmol), $Pd(OAc)_2$ (6.6 mg, 29 μmol), PPh_3 (13 mg, 49 μmol) and K_2CO_3 (270 mg, 1.95 mmol) in 1:1 toluene/ethanol (3 mL) were reacted for 16 hr. Work-up followed by column chromatography eluting with 3% methanol in dichloromethane gave **158c** as a pale yellow oil (176 mg, 59%). $R_f = 0.20$ (1:19 methanol/dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 [6H, t, $^3J = 7.1$ Hz, 2 x CH_3], 3.21 [2H, d, $^2J_{H,P} = 21.7$ Hz, PCH_2], 3.98-4.14 [4H, m, 2 x OCH_2], 7.36 [1H, dd, $^3J_{5',6'} = 7.9$ Hz, $^3J_{4',5'} = 4.8$ Hz, H(5')], 7.39-7.45 [2H, m, H(2) + H(6)], 7.52-7.57 [2H, m, H(3) + H(5)], 7.86 [1H, br d‡, $^3J_{5',6'} = 7.9$ Hz, H(6')], 8.58 [1H, br d‡, $^3J_{4',5'} = 4.8$ Hz, 8.84 [1H, br d‡, $^4J_{2',6'} = 1.1$ Hz, H(2')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.50 [d, $^3J_{C,P} = 6.1$ Hz, 2 x CH_3], 33.60 [d, $^1J_{C,P} = 138.2$ Hz, PCH_2], 62.28 [d, $^2J_{C,P} = 6.8$ Hz, 2 x OCH_2], 123.62 [C(5')], 127.33 [d, $^4J_{C,P} = 3.1$ Hz, C(3) + C(5)], 130.58 [d, $^3J_{C,P} = 6.6$ Hz, C(2) + C(6)], 131.89 [d, $^2J_{C,P} = 9.2$ Hz, C(1)], 134.26 [C(6')], 136.26 [d, $^6J_{C,P} = 1.4$ Hz, C(1')], 136.49 [d, $^5J_{C,P} = 3.8$ Hz, C(4)], 148.33 [d, $^7J_{C,P} = 0.7$ Hz, C(2')], 148.58 [C(4')].

Diethyl 2-(pyrimidin-5-yl)benzylphosphonate (159a)



Using General Method 13, **36k** (320 mg, 1.04 mmol), 5-pyrimidinylboronic acid (155 mg, 1.25 mmol), $Pd(OAc)_2$ (7.0 mg, 31 μmol), PPh_3 (13.7 mg, 52 μmol) and K_2CO_3 (288 mg, 2.08 mmol) in 1:1 toluene/ethanol (3 mL) were reacted for 16 hr. Work-up followed by column chromatography eluting with 3% methanol in dichloromethane gave **159a** as a pale yellow oil (284 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 [6H, t, ^3J = 7.1 Hz, 2 x CH_3], 3.10 [2H, d, $^2J_{H,P}$ = 22.3 Hz, PCH_2], 3.93-4.06 [4H, m, 2 x OCH_2], 7.24 [1H, br d‡, $^3J_{3,4}$ = 7.6 Hz, H(3)], 7.38 [1H, tt, $^3J_{4,5}$ = $^3J_{5,6}$ = 7.6 Hz, $^4J_{3,5}$ = $^5J_{5,P}$ = 1.6 Hz, H(5)], 7.44 [1H, br t‡, $^3J_{3,4}$ = $^3J_{4,5}$ = H(4)], 7.59 [1H, br d‡, $^3J_{5,6}$ = 7.6 Hz, H(6)], 8.83 [2H, s, H(2') + H(6')], 9.24 [1H, s, H(4')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.39 [d, $^3J_{C,P}$ = 5.8 Hz, 2 x CH_3], 30.78 [d, $^1J_{C,P}$ = 139.1 Hz, PCH_2], 62.23 [d, $^2J_{C,P}$ = 6.7 Hz, 2 x OCH_2], 127.52 [d, $^4J_{C,P}$ = 3.5 Hz, C(5)], 129.12 [d, $^5J_{C,P}$ = 3.4 Hz, C(4)], 129.95 [d, $^2J_{C,P}$ = 8.7 Hz, C(1)], 130.62 [d, $^4J_{C,P}$ = 3.1 Hz, C(3)], 131.21 [d, $^3J_{C,P}$ = 4.9 Hz, C(6)], 134.81 [d, $^4J_{C,P}$ = 1.6 Hz, C(1')], 135.14 [d, $^3J_{C,P}$ = 7.7 Hz, C(2)], 157.04 [d, $^5J_{C,P}$ = 1.1 Hz, C(2') + C(6')], 157.59 [br, C(4')].

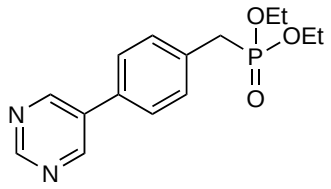
Diethyl 3-(pyrimidin-5-yl)benzylphosphonate (159b)



Using General Method 13, **36l** (250 mg, 0.81 mmol), 5-pyrimidinylboronic acid (150 mg, 1.21 mmol), $Pd(OAc)_2$ (5.5 mg, 24 μmol), PPh_3 (11 mg, 41 μmol) and K_2CO_3 (225 mg, 1.6 mmol) in 1:1 toluene/ethanol (3 mL) were reacted for 16 hr. Work-up followed by column chromatography eluting with 3% methanol in dichloromethane gave **159b** as a pale yellow oil (178 mg, 71%). R_f = 0.06 (2.5% methanol in dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 [6H, t, ^3J = 7.1 Hz, 2 x CH_3], 3.24 [2H, d, $^2J_{H,P}$ = 21.7 Hz, PCH_2], 4.07 [4H, p, ^3J = $^3J_{H,P}$ = 7.1 Hz, 2 x OCH_2], 7.38-7.51 [3H, m, H(4) + H(5) + H(6)], 7.54 [1H, br s‡, H(2)], 8.95 [2H, s, H(2') + H(6')], 9.21 [1H, s, H(4')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.47 [d, $^3J_{C,P}$ = 5.9 Hz, 2 x CH_3], 33.83 [d, $^1J_{C,P}$ = 138.4 Hz, PCH_2], 62.26 [d, $^2J_{C,P}$ = 6.7 Hz, 2 x OCH_2], 125.59 [d, $^5J_{C,P}$ = 3.5 Hz, C(4)], 128.37 [d, $^3J_{C,P}$ = 6.6 Hz, C(2)], 129.67 [d, $^4J_{C,P}$ = 3.0 Hz, C(5)], 130.47 [d, $^3J_{C,P}$ = 6.5 Hz, C(6)], 133.31 [d, $^2J_{C,P}$ = 9.2

Hz, C(1)], 134.08 [C(1')], 134.60 [d, $^4J_{C,P}$ = 3.2 Hz, C(3)], 154.95 [C(2') + C(6')], 157.62 [C(4')].

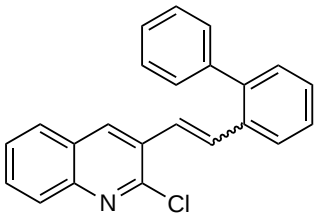
Diethyl 4-(pyrimidin-5-yl)benzylphosphonate (159c)



Using General Method 13, **36m** (320 mg, 1.04 mmol), 5-pyrimidinylboronic acid (155 mg, 1.25 mmol), $Pd(OAc)_2$ (7.0 mg, 31 μmol), PPh_3 (13.7 mg, 52 μmol) and K_2CO_3 (288 mg, 2.08 mmol) in 1:1 toluene/ethanol (3 mL) were reacted for 16 hr. Work-up followed by column chromatography eluting with 3% methanol in dichloromethane gave **159c** as a pale yellow oil (299 mg, 94%). R_f = 0.27 (1:19 methanol/dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 [6H, t, ^3J = 7.1 Hz, 2 x CH_3], 3.22 [2H, d, $^2J_{H,P}$ = 21.9 Hz, PCH_2], 4.00-4.13 [4H, m, 2 x OCH_2], 7.45-7.49 [2H, m, H(2) + H(6)], 7.53-7.57 [2H, m, H(3) + H(5)], 8.95 [2H, s, H(2') + H(6')], 9.20 [1H, s, H(4')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.51 [d, $^3J_{C,P}$ = 5.8 Hz, 2 x CH_3], 33.67 [d, $^1J_{C,P}$ = 138.2 Hz, PCH_2], 62.32 [d, $^2J_{C,P}$ = 6.7 Hz, 2 x OCH_2], 127.17 [d, $^4J_{C,P}$ = 3.0 Hz, C(3)], 130.94 [d, $^3J_{C,P}$ = 6.6 Hz, C(2)], 132.93 [d, $^5J_{C,P}$ = 3.8 Hz, 133.09 [d, $^2J_{C,P}$ = 9.3 Hz, C(1)], 134.00 [d, $^6J_{C,P}$ = 1.5 Hz, C(1')], 154.88 [d, $^7J_{C,P}$ = 0.7 Hz, C(2') + C(6')], 157.58 [C(4')].

6.4.3 Synthesis of 3-position extended 2-chloroquinoline derivatives via Horner-Emmons reaction

3-(2-((1,1'-Biphenyl)-2-yl)vinyl)-2-chloroquinoline (146a)



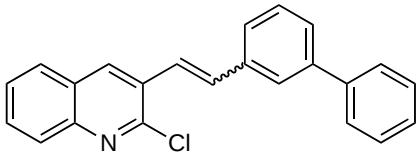
Using General Method 15, **156a** (260 mg, 0.85 mmol), **144** (116 mg, 0.61 mmol), and sodium *tert*-butoxide (140 mg, 1.46 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed by column chromatography eluting with dichloromethane gave **146a** as an off-white solid (161 mg, 78%). R_f = 0.22 (1:1 dichloromethane/hexane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{23}H_{16}{}^{35}ClN/C_{23}H_{16}{}^{37}ClN$: 342.1050/344.1020; found 342.1044/344.1025. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69 [0.3H, d, $^3J_{*A,*B}$ =12.1 Hz, *H(A)], 6.79 [0.3H, d, $^3J_{*A,*B}$ =12.1 Hz,

*H(B)], 7.10 [0.3H, td, d, $^{3}J_{*4',*5'} = {}^{3}J_{*5',*6'}$ =7.7 Hz, $^{4}J_{*3',*5'}$ = 1.4 Hz, *H(5')], 7.15-7.21 [1H, m, H(B) + *H(6')], 7.27 [0.3H, td, $^{3}J_{*3',*4'} = {}^{3}J_{*4',*5'}$ = 7.7 Hz, $^{4}J_{*4',*6'}$ = 1.3 Hz, *H(4')], 7.29-7.52 [9.7H, m, H(A) + H(6) + H(3') + H(4') + H(5') + Ph + *H(5) + *H(6) + *H(8) + *H(3') + *Ph], 7.61-7.68 [1H, m, H(7) + *H(7)], 7.71 [0.7H, br d‡, $^{3}J_{5,6}$ = 8.1 Hz, H(5)], 7.82 [0.7H, br d‡, $^{3}J_{5',6'}$ = 7.5 Hz, H(6')], 7.86 [0.3H, s, *H(4)], 7.96 [0.7H, br d‡, $^{3}J_{7,8}$ = 8.5 Hz, H(8)], 8.07 [0.7H, s, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 124.48 [C(A)], 125.47 [*C(A)], 126.60 [C(6')], **127.03 [*C(6)], 127.06 [C(4a)], 127.12 [*C(4a)], **127.25 [C(6)], **127.41 [C(4'')], 127.45 [*C(5')], 127.47 [C(5')], **127.58 [*C(4'')], 127.61 [*C(5)], 127.67 [C(5)], **127.90 [*C(2'') + *C(6'')], 128.11 [*C(4')], **128.28 [C(2'') + C(6'')], 128.38 [C(8) + *C(8)], 128.54 [C(4')], **129.32 [*C(3'') + *C(5'')], 129.77 [*C(6')], 129.85 [*C(3)], **130.05 [C(3'') + C(5'')], 130.24 [C(7)], 130.30 [*C(7)], 130.43 [*C(3')], **130.54 [C(3')], 130.65 [C(3)], 132.54 [C(B)], 133.63 [*C(B)], 133.94 [C(4)], 134.20 [*C(1')], 134.87 [C(1')], 138.09 [*C(4)], 140.78 [C(1'')], 140.83 [*C(1'')], 141.58 [*C(2')], 141.67 [C(2')], 146.76 [*C(8a)], 146.87 [C(8a)], 150.33 [C(2)], 150.79 [*C(2)].

* Denotes signals corresponding to *Z*-isomer.

** Interpretation of spectra and 2D NMR correlations could not achieve unambiguous assignment of all NMR signals due to overlapped signals in the ^{1}H NMR spectrum.

3-(2-((1,1'-Biphenyl)-3-yl)vinyl)-2-chloroquinoline (146b)

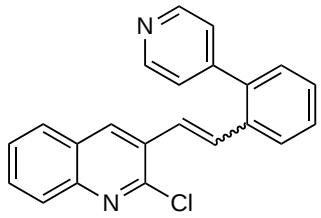


Using General Method 15, **156b** (225 mg, 0.74 mmol), **144** (101 mg, 0.53 mmol), and sodium *tert*-butoxide (122 mg, 1.27 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed by column chromatography eluting with dichloromethane gave **146b** as an off-white solid (130 mg, 72%). R_f = 0.24 (1:1 dichloromethane/hexane).

A sample of (*E*)-3-(2-((1,1'-biphenyl)-3-yl)vinyl)-2-chloroquinoline (*E*-**146b**) was obtained by column chromatography for the purposes of characterisation. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{23}H_{16}{}^{37}ClN$: 344.1020; 344.1024. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24-7.31 [1H, m, H(B)], 7.36-7.44 [1H, m, H(4'')], 7.44-7.52 [3H, m, H(5') + H(3'') + H(5'')], 7.53-7.67 [6H, m, H(A) + H(6) + H(4') + H(6') + H(2'') + H(6'')], 7.68-7.74 [1H, m, H(7)], 7.79 [1H, br s‡, H(2')], 7.86 [1H, br d‡, $^{3}J_{5,6}$ = 8.1 Hz, H(5)], 8.01 [1H, br d‡, $^{3}J_{7,8}$ = 8.4 Hz, H(8)], 8.41 [1H, s, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 124.07 [C(A)], 125.94 [C(6')], 126.09 [C(2')], 127.37 [C(2'') + C(6'')], 127.46 [C(4')], 127.63 [C(6)], 127.71 [*C(5)], 127.72 [*C(4'')], 128.51 [C(8)], 129.01 [C(3'') + C(5'')], 129.44 [C(5')], 130.41 [C(7)], 133.37 [C(B)], 133.95 [C(4)], 137.21 [C(1')], 141.00 [C(1'')], 142.11 [C(3')], 147.04 [C(8a)], 150.40 [C(2)].

*Some ^{13}C NMR signals could not be unambiguously assigned due to close proximity of chemical shifts. The C(4a) signal was not observed; 2D HMBC correlations indicated this signal was overlapped with a signal at 127.7 ppm, but due to close proximity of several signals in this range the C(4a) signal could not be unambiguously assigned.

2-Chloro-3-(2-(pyridin-4-yl)styryl)quinoline (147a)

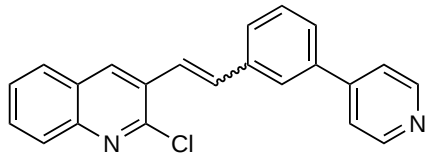


Using General Method 15, **157a** (285 mg, 0.93 mmol), **144** (128 mg, 0.67 mmol), and sodium *tert*-butoxide (154 mg, 1.6 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed by column chromatography eluting with 2% methanol in dichloromethane gave **147a** as an off-white solid (142 mg, 62%). R_f = 0.16 (2.5% methanol in dichloromethane). Samples of each isomer were isolated by column chromatography for the purposes of characterisation.

*(*E*)-2-Chloro-3-(2-(pyridin-4-yl)styryl)quinoline (*E-***147a***):* MP: 174-180°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{15}{}^{35}ClN_2/C_{22}H_{15}{}^{37}ClN_2$: 343.1002/345.0973; found 343.1000/345.1983. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 [1H, d, $^3J_{A,B}$ = 16.1 Hz, H(B)], 7.32-7.39 [3H, m, H(3') + H(2'') + H(6'')], 7.41-7.56 [4H, m, H(A) + H(6) + H(4') + H(5')], 7.67 [1H, t, $^3J_{7,8}$ = 8.3 Hz, H(7)], 7.75 [1H, d, $^3J_{5,6}$ = 8.1 Hz, H(5)], 7.85 [1H, d, $^3J_{5',6'}$ = 7.8 Hz, H(6')], 7.97 [1H, d, $^3J_{7,8}$ = 8.3 Hz, H(8)], 8.09 [1H, s, H(4)], 8.66-8.74 [2H, m, H(3'') + H(5'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 124.86 [C(2'') + C(6'')], 125.70 [C(A)], 126.94 [C(6')], 127.41 [C(6)], 127.47 [C(4a)], 127.73 [C(5)], 128.37 [C(8)], 128.78 [C(4')], 129.12 [C(5')], 130.01 [C(3')], 130.13 [C(3)], 130.48 [C(7)], 131.24 [C(B)], 134.00 [C(4)], 134.79 [C(1')], 138.69 [C(2')], 146.99 [C(8a)], 148.64 [C(1'')], 149.93 [C(3'') + C(5'')], 150.15 [C(2)].

*(*Z*)-2-Chloro-3-(2-(pyridin-4-yl)styryl)quinoline (*Z-***147a***):* HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{15}{}^{35}ClN_2/C_{22}H_{15}{}^{37}ClN_2$: 343.1002/345.0973; found 343.1000/345.1983. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.76 and 6.79 [2H, *AB*, *A*:br d‡, *B*:d, $^3J_{A,B}(J_{AB})$ = 12.1 Hz, H(A) + H(B)], 7.17-7.26 [4H, m, H(5') + H(6') + H(2'') + H(6'')], 7.29-7.36 [2H, m, H(3') + H(4')], 7.44-7.53 [2H, m, H(5) + H(6)], 7.69 [1H, ddd, $^3J_{7,8}$ = 8.5 Hz, $^3J_{6,7}$ = 6.7 Hz, $^4J_{5,7}$ = 1.6 Hz, H(7)], 7.79 [1H, s, H(4)], 7.98 [1H, d, $^3J_{7,8}$ = 8.5 Hz, H(8)], 8.57-8.63 [2H, m, H(3'') + H(5'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 124.12 [C(2'') + C(6'')], 126.80 [C(A)], 126.97 [C(4a)], 127.21 [C(6)], 127.58 [C(5)], 128.41 [C(8)], 128.45 [C(4')], 128.76 [C(5')], 129.51 [C(3)], 130.07 [C(3')], 130.14 [C(6')], 130.55 [C(7)], 132.59 [C(B)], 134.31 [C(1')], 138.19 [C(4)], 138.68 [C(2')], 146.88 [C(8a)], 148.55 [C(1'')], 149.87 [C(3'') + C(5'')], 150.62 [C(2)].

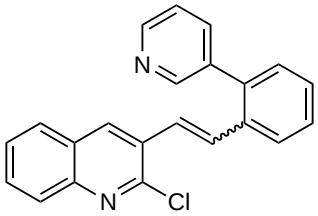
2-Chloro-3-(3-(pyridin-4-yl)styryl)quinoline (147b)



Using General Method 15, **157b** (200 mg, 0.66 mmol), **144** (90 mg, 0.47 mmol), and sodium *tert*-butoxide (108 mg, 1.12 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed by column chromatography eluting with dichloromethane gave **147b** as an off-white solid (103 mg, 64%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{15}{}^{35}ClN_2/C_{22}H_{15}{}^{37}ClN_2$: 343.1002/345.0973; found 343.0995/345.0975. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81 [0.25H, br d‡, $^3J_{*A,*B} = 12.1$ Hz, *H(A)], 6.92 [0.25H, d, $^3J_{*A,*B} = 12.1$ Hz, *H(B)], 7.19-7.31 [1.75H, m, H(B) + *H(5') + *H(6') + *H(2'') + *H(6'')], 7.42-7.46 [0.5H, m, *H(2') + *H(4')], 7.47 [0.25H, ddd, $^3J_{*5,*6} = 8.1$ Hz, $^3J_{*6,*7} = 6.9$ Hz, $^4J_{*6,*8} = 1.1$ Hz, *H(6)], 7.53 [0.75H, t, $^3J_{4',5'} = {}^3J_{5',6'} = 7.7$ Hz, H(5')], 7.53-7.63 [4H, m, H(A) + H(6) + H(4') + H(2'') + H(6'') + *H(5)], 7.67 [0.75H, br d‡, $^3J_{5',6'} = 7.7$ Hz, H(6')], 7.69-7.73 [1H, m, H(7) + *H(7)], 7.80 [0.75H, br s‡, H(2')], 7.85 [0.75H, br d‡, $^3J_{5,6} = 8.0$ Hz, H(5)], 7.98-8.04 [1.25H, H(8) + *H(4) + *H(8)], 8.40 [0.75H, s, H(4)], 8.51-8.54 [0.5H, m, *H(3'') + *H(5'')], 8.68-8.72 [1.5H, m, H(3'') + H(5'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 121.48 [*C(2'') + *C(6'')], 121.80 [C(2'') + C(6'')], 124.65 [C(A)], 125.82 [C(2')], 126.41 [*C(4')], 126.47 [*C(A)], 127.02 [*C(4a)], 127.24 [C(6)], 127.31 [*C(6)], 127.46 [C(6')], 127.49 [C(4')], 127.50 [C(4a)], 127.60 [*C(5)], 128.42 [*C(8)], 128.47 [C(8)], 129.41 [*C(5')], 129.51 [*C(6')], 129.78 [C(5')], 129.91 [*C(3)], 130.13 [C(3)], 130.51 [C(7)], 130.66 [*C(7)], 132.70 [C(B)], 132.90 [*C(B)], 134.04 [C(4)], 136.80 [*C(1')], 137.61 [C(1')], 138.48 [*C(4)], 138.53 [*C(3')], 139.03 [C(3')], 147.07 [br, C(8a) + *C(8a)], 147.78 [*C(1'')]. 150.25 [C(2)], 150.33 [*C(3'') + *C(5'')], 150.49 [C(3'') + C(5'')], 150.59 [*C(2)].

*Denotes signals corresponding to the *Z*-isomer of the product.

2-Chloro-3-(2-(pyridin-3-yl)styryl)quinoline (148a)



Using General Method 15, **158a** (267 mg, 0.87 mmol), **144** (120 mg, 0.63 mmol), and sodium *tert*-butoxide (144 mg, 1.50 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed by column chromatography eluting with dichloromethane gave **148a** as a yellow

solid (199 mg, 93%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{15}{}^{35}ClN_2/C_{22}H_{15}{}^{37}ClN_2$: 343.1002/345.0973; found 343.0996/345.0976. Pure samples of each isomer were separated by column chromatography for characterisation.

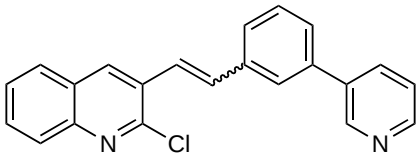
*(E)-2-Chloro-3-(2-(pyridin-3-yl)styryl)quinoline (*E-***148a***):* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 [1H, d, $^3J_{A,B} = 16.1$ Hz, H(B)], 7.34-7.41 [2H, m, H(3') + H(5")], 7.42-7.55 [4H, m, H(6) + H(A) + H(4') + H(5')], 7.67 [1H, ddd, $^3J_{7,8} = 8.4$ Hz, $^3J_{6,7} = 7.0$ Hz, $^4J_{5,7} = 1.4$ Hz, H(7)], 7.71-7.77 [2H, m, H(5) + H(6")], 7.86 [1H, br d‡, $^3J_{5',6'}$ = H(6')], 7.97 [1H, d, $^3J_{7,8} = 8.4$ Hz, H(8)], 8.10 [1H, s, H(4)], 8.65 [1H, dd, $^3J_{4",5"} = 4.8$ Hz, $^4J_{4",6"} = 1.6$ Hz, H(4")], 8.71 [1H, br d‡, $^4J_{2",6"} = 2.2$ Hz, H(2")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 123.25 [C(5")], 125.71 [C(A)], 126.91 [C(6')], 127.36 [C(6)], 127.50 [C(4a)], 127.72 [C(5)], 128.38 [C(8)], 128.76 [**C(4')], 128.78 [*C(5')], 130.27 [C(3)], 130.42 [C(7)], 130.57 [C(3')], 131.41 [C(B)], 134.07 [C(4)], 135.24 [C(1')], 136.41 [C(1")], 137.23 [C(6")], 137.79 [C(2')], 146.98 [C(8a)], 148.78 [C(4")], 150.18 [C(2)], 150.49 [C(2")].

*Some ^{13}C NMR signals could not be unambiguously assigned due to close proximity of chemical shifts.

*(Z)-2-Chloro-3-(2-(pyridin-3-yl)styryl)quinoline (*Z-***148a***):* ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74 [1H, d, $^3J_{A,B} = 12.0$ Hz, H(A)], 6.81 [1H, d, $^3J_{A,B} = 12.0$ Hz, H(B)], 7.18-7.36 [5H, m, H(3') + H(4') + H(5') + H(6') + H(5")], 7.42-7.54 [3H, m, H(5) + H(6) + H(6")], 7.68 [1H, ddd, $^3J_{7,8} = 8.4$ Hz, $^3J_{6,7} = 6.7$ Hz, $^4J_{5,7} = 1.6$ Hz, H(7)], 7.78 [1H, s, H(4)], 7.97 [1H, d, $^3J_{7,8} = 8.4$ Hz, H(8)], 8.53-8.61 [2H, m, H(2") + H(4")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 123.12 [C(5")], 126.65 [C(A)], 126.93 [C(4a)], 127.16 [C(6)], 127.55 [C(5)], 128.35 [*C(4') or C(5')], 128.37 [C(8)], 128.41 [*C(4') or C(5')], 129.51 [C(3)], 130.06 [*C(3') or C(6')], 130.49 [*C(3') or C(6')], 130.50 [C(7)], 132.59 [C(B)], 134.57 [C(1')], 136.26 [C(6")], 136.45 [C(1")], 137.72 [C(2')], 138.09 [C(4)], 146.81 [C(8a)], 148.63 [C(4")], 150.03 [C(2")], 150.58 [C(2)].

*Interpretation of spectra and 2D NMR correlations could not achieve unambiguous assignment of all NMR signals due to overlapped signals in the ^{1}H NMR spectrum.

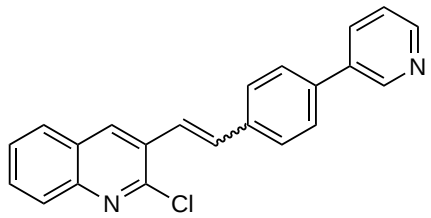
2-Chloro-3-(3-(pyridin-3-yl)styryl)quinoline (148b)



Using General Method 15, **158b** (164 mg, 0.54 mmol), **144** (94 mg, 0.49 mmol), and sodium *tert*-butoxide (66 mg, 0.69 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed by column chromatography eluting with dichloromethane gave (*E/Z*)-**148b** as an off-white solid (145 mg, 86%).

A sample of almost entirely (*E*)-2-chloro-3-(3-(pyridin-3-yl)styryl)quinoline (*E*-**148b**, 19:1 ratio of *E*/*Z* isomers) was separated by column chromatography for the purposes of characterisation. R_f = 0.19 (2% methanol in dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{15}{}^{35}ClN_2/C_{22}H_{15}{}^{37}ClN_2$: 343.1002/345.0973; found 343.0995/345.0974. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 [1H, d, $^3J_{A,B}$ = 16.2 Hz, H(B)], 7.41 [1H, dd, $^3J_{5'',6''}$ = 7.8 Hz, $^3J_{4'',5''}$ = 4.8 Hz, H(5'')], 7.51-7.64 [4H, m, H(A) + H(6) + H(4') + H(5')]], 7.66 [1H, br d‡, $^3J_{5',6'}$ = H(6')], 7.72 [1H, br dd‡, $^3J_{7,8}$ = 8.3 Hz, $^3J_{6,7}$ = 7.0 Hz, H(7)], 7.77 [1H, br s‡, H(2')], 7.86 [1H, d, $^3J_{5,6}$ = 8.1 Hz, H(5)], 7.93 [1H, br d‡, $^3J_{5'',6''}$ = 7.9 Hz, H(6'')], 8.01 [1H, br d‡, $^3J_{7,8}$ = 8.3 Hz, H(8)], 8.42 [1H, s, H(4)], 8.64 [1H, br d‡, $^3J_{4'',5''}$ = 4.8 Hz, H(4'')], 8.91 [1H, br d‡, $^4J_{2'',6''}$ = 1.7 Hz, H(2'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 123.76 [C(5'')], 124.55 [C(A)], 126.05 [C(2')], 126.62 [C(6')], 127.48 [C(4')], 127.50 [C(6)], 127.65 [C(4a)], 127.72 [C(5)], 128.50 [C(8)], 129.77 [C(5')], 130.24 [C(3)], 130.51 [C(7)], 132.89 [C(B)], 134.05 [C(4)], 134.57 [C(6'')], 136.46 [C(1')], 137.58 [C(1'')], 138.73 [C(3')], 147.09 [C(8a)], 148.51 [C(2'')], 148.93 [C(4'')], 150.32 [C(2)].

2-Chloro-3-(4-(pyridin-3-yl)styryl)quinoline (148c)



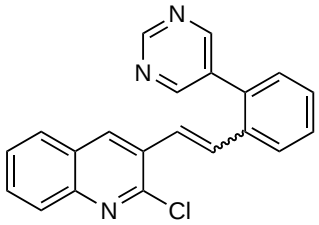
Using General Method 15, **158c** (291 mg, 0.95 mmol), **144** (152 mg, 0.79 mmol), and sodium *tert*-butoxide (138 mg, 1.44 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed by column chromatography eluting with 1% methanol in dichloromethane gave **148c** as a yellow solid (212 mg, 78%). R_f = 0.08 (2% methanol in dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{15}{}^{35}ClN_2/C_{22}H_{15}{}^{37}ClN_2$: 343.1002/345.0973; found 343.0999/345.0981. ^{1}H NMR (500 MHz, $CDCl_3$): δ ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.79 [0.2H, d, $^3J_{*A,*B}$ = 12.1 Hz, *H(A)], 6.89 [0.2H, d, $^3J_{*A,*B}$ = 12.1 Hz, *H(B)], 7.23 [0.8H, d, $^3J_{A,B}$ = 16.2 Hz, H(B)], 7.28-7.34 [0.6H, m, *H(2') + *H(6') + *H(5'')], 7.38 [0.8H, dd, $^3J_{5'',6''}$ = 7.9 Hz, $^3J_{4'',5''}$ = 4.8 Hz, H(5'')], 7.40-7.44 [0.4H, m, *H(3') + *H(5')], 7.47 [0.2H, br t‡, $^3J_{*5,*6}$ = $^3J_{*6,*7}$ = 7.6 Hz, *H(6)], 7.53-7.73 [6.2H, m, H(A) + H(6) + H(7) + H(2') + H(3') + H(5') + H(6') + *H(5) + *H(7) + *H(8)], 7.81 [0.2H, dt, $^3J_{*5'',*6''}$ = 7.9 Hz, $^4J_{*2'',*6''}$ = $^4J_{*4'',*6''}$ = 2.1 Hz, *H(6'')], 7.84 [0.8H, br d‡, $^3J_{5,6}$ = 7.9 Hz, H(5)], 7.90 [0.8H, ddd, $^3J_{5'',6''}$ = 7.9 Hz, $^4J_{2'',6''}$ = 2.0 Hz, $^4J_{4'',6''}$ = 1.7 Hz, H(6'')], 7.98-8.04 [1H, m, H(8) + *H(4)], 8.39 [0.8H, s, H(4)], 8.56 [0.2H, br d‡, $^3J_{*4'',*5''}$ = 4.8 Hz, *H(4'')], 8.61 [0.8H, br d‡, $^3J_{4'',5''}$ = 4.8 Hz, H(4'')], 8.80 [0.2H, br d‡, $^4J_{*2'',*6''}$ = 2.1 Hz, *H(2'')], 8.89 [0.8H, br d‡, $^4J_{2'',6''}$ = 2.1 Hz, H(2'')].

* Denotes signals corresponding to *Z*-isomer.

Interpretation of spectra and 2D NMR correlations could not achieve unambiguous assignment of all ^{13}C NMR signals due to overlapped signals in the ^{1}H and ^{13}C NMR spectra.

A sample of pure (*E*)-2-chloro-3-(4-(pyridin-3-yl)styryl)quinoline (*E*-**148c**) was isolated by column chromatography for the purposes of characterisation. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 [1H, d, $^{3}J_{A,B}$ = 16.2 Hz, H(B)], 7.38 [1H, ddd, $^{3}J_{5'',6''}$ = 7.9 Hz, $^{3}J_{4'',5''}$ = 4.8 Hz, $^{4}J_{2'',5''}$ = 0.8 Hz, H(5'')], 7.53-7.59 [2H, m, H(A) + H(6)], 7.61-7.65 [2H, m, H(3') + H(5')], 7.67-7.73 [3H, m, H(7) + H(2') + H(6')], 7.84 [1H, br d‡, $^{3}J_{5,6}$ = 7.9 Hz, H(5)], 7.90 [1H, ddd, $^{3}J_{5'',6''}$ = 7.9 Hz, $^{4}J_{2'',6''}$ = 2.0 Hz, $^{4}J_{4'',6''}$ = 1.7 Hz, H(6'')], 8.00 [1H, br d‡, $^{3}J_{7,8}$ = 8.2 Hz, H(8)], 8.39 [1H, s, H(4)], 8.61 [1H, dd, $^{3}J_{4'',5''}$ = 4.8 Hz, $^{4}J_{4'',6''}$ = 1.7 Hz, H(4'')], 8.89 [1H, br d‡, $^{4}J_{2'',6''}$ = 2.0 Hz, H(2'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 123.72 [C(5'')], 124.25 [C(A)], 127.46 [C(6)], 127.62 [C(3') + C(5')], 127.62 [C(4a)], 127.68 [C(5)], 127.81 [C(2') + C(6')], 128.47 [C(8)], 130.24 [C(3)], 130.44 [C(7)], 132.51 [C(B)], 133.90 [C(4)], 134.21 [C(6'')], 136.03 [C(1'')], 136.57 [C(1')], 137.95 [C(4')], 147.02 [C(8a)], 148.30 [C(2'')], 148.83 [C(4'')], 150.30 [C(2)].

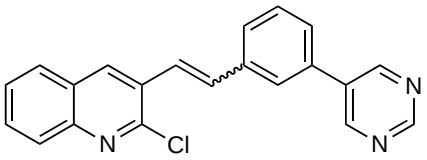
2-Chloro-3-(2-(pyrimidin-5-yl)styryl)quinoline (149a)



Using General Method 15, **159a** (264 mg, 0.86 mmol), **144** (118 mg, 0.62 mmol), and sodium *tert*-butoxide (142 mg, 1.48 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed by column chromatography eluting with dichloromethane gave **149a** as an off-white solid (114 mg, 54%).

A sample of (*Z*)-2-chloro-3-(2-(pyrimidin-5-yl)styryl)quinoline (*Z*-**149a**) was isolated by chromatography for the purposes of characterisation. MP: degraded 90°C. HRMS (ESI+) $[M+H]^{+}$ calcd. for $C_{21}H_{14}{}^{35}ClN_3/C_{21}H_{14}{}^{37}ClN_3$: 344.0955/346.0925; found 344.0948/346.0938. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.79 and 6.83 [2H, *AB*, *A*:d, *B*:d, $^{3}J_{A,B}(J_{AB})$ = 12.0 Hz, H(A) + H(B)], 7.24-7.41 [4H, m, H(3') + H(4') + H(5') + H(6')], 7.43-7.51 [2H, m , H(5) + H(6)], 7.66-7.72 [2H, m, H(4) + H(7)], 7.98 [1H, br d‡, $^{3}J_{7,8}$ = 8.5 Hz, H(8)], 8.58 [2H, s, H(2'') + H(6'')], 9.18 [1H, s, H(4'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 126.80 [C(4a)], 127.33 [C(6)], 127.49 [C(5)], 127.78 [C(A)], 128.53 [C(8)], 128.75 [C(4')], 129.12 [C(3)], 129.31 [C(5')], 130.35 [C(3')], 130.38 [C(6')], 130.73 [C(7)], 131.66 [C(B)], 133.89 [C(2')], 134.44 [C(1'')], 134.81 [C(1')], 138.12 [C(4)], 146.91 [C(8a)], 150.32 [C(2)], 156.45 [C(2'') + C(6'')], 157.57 [C(4'')].

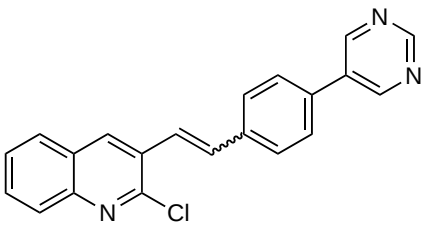
2-Chloro-3-(3-(pyrimidin-5-yl)styryl)quinoline (149b)



Using General Method 15, **159b** (234 mg, 0.76 mmol), **144** (122 mg, 0.64 mmol), and sodium *tert*-butoxide (147 mg, 1.6 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed by column chromatography eluting with dichloromethane gave **149b** as a yellow solid (218 mg, 100%). R_f = 0.18 (2.5% methanol in dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{14}{}^{35}ClN_3/C_{21}H_{14}{}^{37}ClN_3$: 344.0955/346.0925; found 344.0951/346.0939. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 [0.2H, d, $^3J_{A,B}$ = 12.1 Hz, *H(A)], 6.92 [0.2H, d, $^3J_{A,B}$ = 12.1 Hz, *H(B)], 7.21-7.29 [1H, m, H(B) + *H(6')], 7.32 [0.2H, t, $^3J_{4',5'} = {}^3J_{5',6'}$ = 7.8 Hz, *H(5')], 7.36-7.43 [0.4H, m, *H(2') + *H(4')], 7.48 [0.2H, ddd, $^3J_{5,6}$ = 8.1 Hz, $^3J_{6,7}$ = 6.9 Hz, $^4J_{6,8}$ = 1.0 Hz, *H(6)], 7.50-7.64 [3.4H, m, *H(5) + H(6) + H(A) + H(4') + H(5')], 7.66-7.76 [2.6H, m, H(7) + *H(7) + H(2') + H(6')], 7.85 [0.8H, d, $^3J_{5,6}$ = 8.1 Hz, H(5)], 7.96-8.04 [1.2H, m, *H(4) + H(8) + *H(8)], 8.40 [0.8H, s, H(4)], 8.72 [0.4H, s, *H(2'') + *H(6'')], 9.00 [1.6H, s, H(2'') + H(6'')], 9.15 [0.2H, s, *H(4'')], 9.25 [0.8H, s, H(4'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 124.99 [C(A)], 125.79 [C(2')], 126.38 [*C(4')], 126.78 [*C(A)], 126.92 [*C(4a)], 127.12 [C(4')], 127.32 [C(6')], 127.36 [*C(6)], 127.41 [*C(2')], 127.49 [C(6)], 127.55 [C(4a)], 127.61 [*C(5)], 127.68 [C(5)], 128.46 [C(8) + *C(8)], 129.35 [*C(6')], 129.68 [*C(3)], 129.69 [*C(5')], 129.96 [C(3)], 130.07 [C(5')], 130.55 [C(7)], 130.72 [*H(7)], 132.35 [C(B)], 132.58 [*C(B)], 133.93 [C(1'')], 134.07 [C(4)], 134.14 [C(1'')], 134.77 [*C(3')], 135.13 [C(3')], 137.21 [*C(1')], 137.93 [C(1')], 138.40 [*C(4)], 147.06 [*C(8a)], 147.09 [C(8a)], 150.19 [C(2)], 150.48 [*C(2)], 154.82 [*C(2'') + *C(6'')], 155.05 [C(2'') + C(6'')], 157.70 [*C(4'')], 157.86 [C(4'')].

* denotes signals corresponding to the *Z*-isomer, minor product.

2-Chloro-3-(4-(pyrimidin-5-yl)styryl)quinoline (149c)



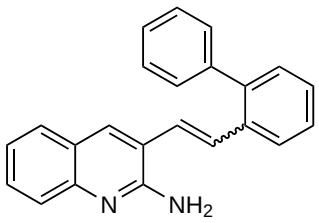
Using General Method 15, **159c** (299 mg, 0.98 mmol), **144** (134 mg, 0.70 mmol), and sodium *tert*-butoxide (162 mg, 1.69 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed

by column chromatography eluting with dichloromethane gave **149c** as a yellow solid (188 mg, 78%).

A sample of (*E*)-2-chloro-3-(4-(pyrimidin-5-yl)styryl)quinoline (*E*-**149c**) was isolated by chromatography for the purposes of characterisation. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{14}{}^{35}ClN_3/C_{21}H_{14}{}^{37}ClN_3$: 344.0955/346.0925; found 344.0950/346.0931. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 [1H, d, $^3J_{A,B} = 16.2$ Hz, H(B)], 7.55-7.65 [4H, m, H(A) + H(6) + H(3') + H(5')], 7.67-7.75 [3H, m, H(7) + H(2') + H(6')], 7.84 [1H, br d‡, $^3J_{5,6} = 7.9$ Hz, H(5)], 7.99 [1H, br d‡, $^3J_{7,8} = 8.4$ Hz, H(8)], 8.38 [1H, s, H(4)], 8.98 [2H, s, H(2'') + H(6'')], 9.22 [1H, s, H(4'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 124.85 [C(A)], 127.41 [C(3') + C(5')], 127.48 [C(6)], 127.54 [C(4a)], 127.67 [C(5)], 128.04 [C(2') + C(6')], 128.44 [C(8)], 129.98 [C(3)], 130.52 [C(7)], 132.08 [C(B)], 133.73 [C(1'')], 133.98 [C(4)], 134.20 [C(4')], 137.43 [C(1')], 147.04 [C(8a)], 150.20 [C(2)], 154.78 [C(2'') + C(6'')], 157.70 [C(4'')].

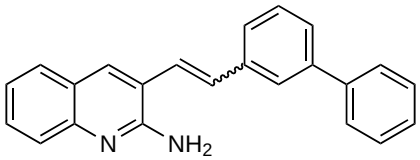
6.4.4 Synthesis of 3-position biaryl-extended 2-aminoquinoline derivatives

Attempted synthesis of 3-(2-((1,1'-biphenyl)-2-yl)vinyl)quinolin-2-amine (160a)



Using General Method 11, **146a** (140 mg, 0.41 mmol) was treated with LiHMDS solution (1.0 M in THF, 0.90 mL, 0.90 mmol), $Pd(dba)_2$ (2.4 mg, 4.0 μmol) and DavePhos (1.9 mg, 4.9 μmol) in 1,4-dioxane (2 mL). Work-up as specified gave a crude mixture which could not be purified. Analysis of the ^{1}H NMR spectrum did not identify signals consistent with the desired product.

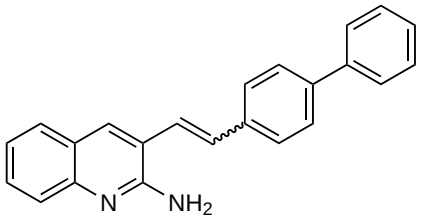
Attempted synthesis of 3-(2-((1,1'-biphenyl)-3-yl)vinyl)quinolin-2-amine (160b)



Using General Method 11, **146b** (111 mg, 0.32 mmol) was treated with LiHMDS solution (1.0 M in THF, 710 μL, 0.71 mmol), $Pd(dba)_2$ (1.9 mg, 3.2 μmol) and DavePhos (1.5 mg, 3.9 μmol) in 1,4-dioxane (2 mL). Work-up as specified gave a crude mixture which could not

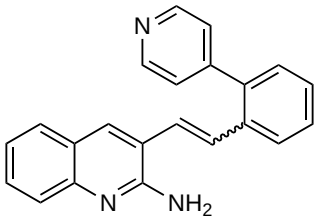
be purified. Analysis of the ^{1}H NMR spectrum did not identify signals consistent with the desired product.

Attempted synthesis of 3-(2-((1,1'-biphenyl)-4-yl)vinyl)quinolin-2-amine (160c)



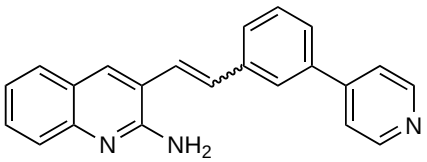
Using General Method 11, **146c** (156 mg, 0.46 mmol) was treated with LiHMDS solution (1.0 M in THF, 1.0 mL, 1.0 mmol), $Pd(dba)_2$ (2.6 mg, 4.5 μmol) and DavePhos (2.2 mg, 5.6 μmol) in 1,4-dioxane (2 mL). Work-up as specified gave a crude mixture which could not be purified. Analysis of the ^{1}H NMR spectrum did not identify signals consistent with the desired product.

Attempted synthesis of 3-(2-(pyridin-4-yl)styryl)quinolin-2-amine (161a)



Using General Method 11, **147a** (132 mg, 0.39 mmol) was treated with LiHMDS solution (1.0 M in THF, 850 μL, 0.85 mmol), $Pd(dba)_2$ (2.2 mg, 3.9 μmol) and DavePhos (1.8 mg, 4.6 μmol) in 1,4-dioxane (2 mL). Work-up as specified gave a crude mixture which could not be purified. Analysis of the ^{1}H NMR spectrum did not identify signals consistent with the desired product.

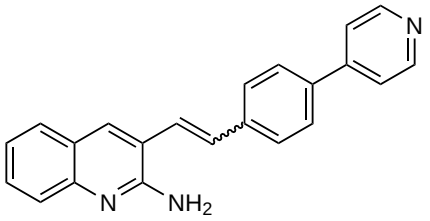
Attempted synthesis of 3-(3-(pyridin-4-yl)styryl)quinolin-2-amine (161b)



Using General Method 11, **147b** (65 mg, 0.19 mmol) was treated with LiHMDS solution (1.0 M in THF, 420 μL, 0.42 mmol), $Pd(dba)_2$ (2.4 mg, 4.2 μmol) and DavePhos (0.9 mg, 2.3 μmol) in 1,4-dioxane (2 mL). Work-up as specified gave a crude mixture which could not be

purified. Analysis of the ^{1}H NMR spectrum did not identify signals consistent with the desired product.

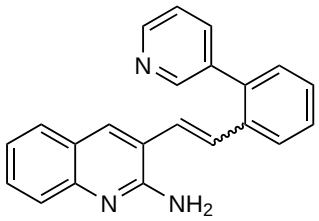
3-(4-(Pyridin-4-yl)styryl)quinolin-2-amine (161c)



Using General Method 11, **147c** (216 mg, 0.63 mmol) was treated with LiHMDS solution (1.0 M in THF, 1.4 mL, 1.4 mmol), $Pd(dba)_2$ (3.6mg, 6.3 μmol) and DavePhos (3.0 mg, 7.6 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 7.5% methanol in dichloromethane gave a crude mixture containing **161c** as a brown oil. R_f = 0.32 (7.5% methanol/dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.13-5.45 [2H, m, NH_2 + *NH_2], 6.61 [0.6H, d, $^3J_{*A,*B}$ = 12.1 Hz, *H(A)], 6.89 [0.6H, d, $^3J_{*A,*B}$ = 12.1 Hz, *H(B)], 7.16-7.77 [10.8H, m, H(A) + H(B) + Ar H + *Ar H], 7.81 [0.6H, s, *H(4)], 8.07 [0.4H, s, H(4)], 8.55-8.72 [2H, m, H(3") + H(5") + *H(3") + *H(5")].

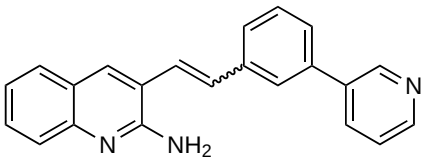
* Denotes signals corresponding to Z-isomer.

Attempted synthesis of 3-(2-(pyridin-3-yl)styryl)quinolin-2-amine (162a)



Using General Method 11, **148a** (162 mg, 0.47 mmol) was treated with LiHMDS solution (1.0 M in THF, 1.0 mL, 1.0 mmol), $Pd(dba)_2$ (2.7 mg, 4.7 μmol) and DavePhos (2.2 mg, 5.7 μmol) in 1,4-dioxane (2 mL). Work-up as specified gave a crude mixture which could not be purified. Analysis of the ^{1}H NMR spectrum did not identify signals consistent with the desired product.

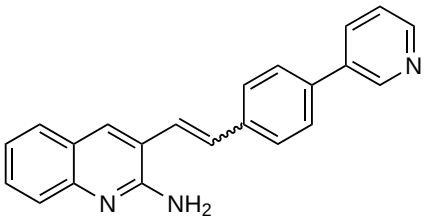
3-(3-(Pyridin-3-yl)styryl)quinolin-2-amine (162b)



Using General Method 11, **148b** (171 mg, 0.50 mmol) was treated with LiHMDS solution (1.0 M in THF, 1.1 mL, 1.1 mmol), $Pd(dba)_2$ (2.9 mg, 5.0 μmol) and DavePhos (2.4 mg, 6.1 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave **162b** as a yellow oil (18 mg, 11%).

A sample containing largely (*E*)-3-(3-(pyridin-3-yl)styryl)quinolin-2-amine (*E*-**162b**) was isolated by column chromatography for the purposes of characterisation. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{17}N_3$: 324.1501; found 324.1495. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.05 [2H, br s, NH_2], 7.20 and 7.22 [2H, *AB*, *A*:d, *B*:d, $^3J_{A,B}(J_{AB}) = 16.5$ Hz, H(A) + H(B)], 7.29 [1H, t, $^3J_{5,6} = {}^3J_{6,7} = 7.6$ Hz, H(6)], 7.39 [1H, dd, $^3J_{5'',6''} = 7.8$ Hz, $^3J_{4'',5''} = 4.8$ Hz, H(5'')], 7.49-7.62 [4H, m, H(7) + H(4') + H(5') + H(6')], 7.65-7.71 [2H, m, H(5) + H(8)], 7.72 [1H, br s‡, H(2')], 7.91 [1H, br d‡, $^3J_{5'',6''} = 7.8$ Hz, H(6'')], 8.05 [1H, s, H(4)], 8.63 [1H, br dd‡, $^3J_{4'',5''} = 4.8$ Hz, $^4J_{4'',6''} = 0.9$ Hz, H(4'')], 8.89 [1H, br d‡, $^4J_{2'',6''} = 1.6$ Hz, H(2'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 121.42 [C(3)], 123.31 [C(6)], 123.68 [C(A)], 123.74 [C(5'')], 124.54 [C(4a)], 125.72 [C(2')], 125.81 [C(8)], 126.42 [C(6')], 127.24 [C(4')], 127.70 [C(5)], 129.75 [C(5')], 129.94 [C(7)], 133.05 [C(B)], 134.55 [C(6'')], 134.60 [C(4)], 136.47 [C(1'')], 137.74 [C(1')], 138.72 [C(3')], 147.22 [C(8a)], 148.49 [C(2'')], 148.93 [C(4'')], 155.35 [C(2)].

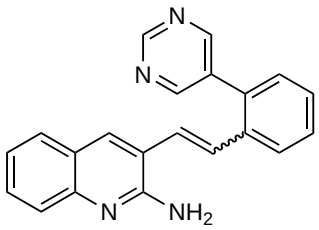
3-(4-(Pyridin-3-yl)styryl)quinolin-2-amine (162c)



Using General Method 11, **148c** (180 mg, 0.53 mmol) was treated with LiHMDS solution (1.0 M in THF, 1.2 mL, 1.2 mmol), $Pd(dba)_2$ (3.0 mg, 5.3 μmol) and DavePhos (2.5 mg, 6.3 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave a sample of crude **162c** as a brown oil (18 mg, <5%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.89-5.17 [2H, m, NH_2 + *NH_2], 6.60 [0.8H, d, $^3J_{*A,*B} = 12.1$ Hz, *H(A)], 6.86 [0.8H, d, $^3J_{*A,*B} = 12.1$ Hz, *H(B)], 7.14-7.82 [10.6H, m, H(A) + H(B) + Ar H + *Ar H], 8.03 [0.2H, s, H(4)], 8.51-8.65 [1H, m, H(4'') + *H(4'')], 8.79 [0.8H, d, $^4J_{*2'',*6''} = 1.5$ Hz, *H(2'')], 8.89 [0.8H, d, $^4J_{2'',6''} = 1.4$ Hz, H(2'')].

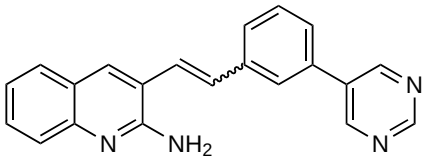
* Denotes signals corresponding to Z-isomer.

Attempted synthesis of 3-(2-(pyrimidin-5-yl)styryl)quinolin-2-amine (163a)



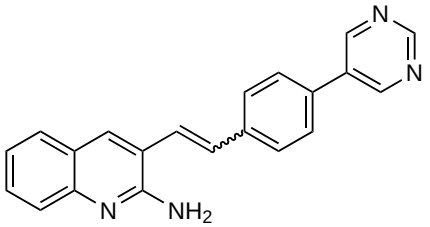
Using General Method 11, **149a** (70 mg, 0.20 mmol) was treated with LiHMDS solution (1.0 M in THF, 450 μL, 0.45 mmol), $Pd(dba)_2$ (1.2 mg, 2.0 μmol) and DavePhos (1.0 mg, 2.4 μmol) in 1,4-dioxane (2 mL). Work-up as specified gave a crude mixture which could not be purified. Analysis of the ^{1}H NMR spectrum did not identify signals consistent with the desired product.

3-(3-(Pyrimidin-5-yl)styryl)quinolin-2-amine (163b)



Using General Method 11, **149b** (249 mg, 0.72 mmol) was treated with LiHMDS solution (1.0 M in THF, 1.6 mL, 1.6 mmol), $Pd(dba)_2$ (4.2 mg, 7.2 μmol) and DavePhos (3.4 mg, 8.6 μmol) in 1,4-dioxane (2 mL). Work-up as specified and column chromatography on silica gel eluting with 19:1 dichloromethane/methanol gave a crude mixture as a brown oil (19 mg, $<$5%), which could not be purified. ^{1}H NMR analysis of the crude mixture was used to identify signals consistent with the desired product **163b**. Due to the large number of impurities present, assignment of the spectrum was not possible.

Attempted synthesis of 3-(4-(pyrimidin-5-yl)styryl)quinolin-2-amine (163c)

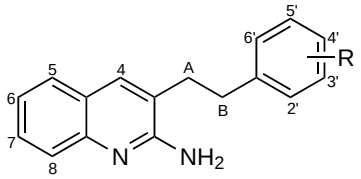


Using General Method 11, **149c** (100 mg, 0.29 mmol) was treated with LiHMDS solution (1.0 M in THF, 640 μL, 0.64 mmol), $Pd(dba)_2$ (1.7 mg, 2.9 μmol) and DavePhos (1.4 mg,

3.5 μmol) in 1,4-dioxane (2 mL). Work-up as specified gave a crude mixture which could not be purified. Analysis of the ^{1}H NMR spectrum did not identify signals consistent with the desired product.

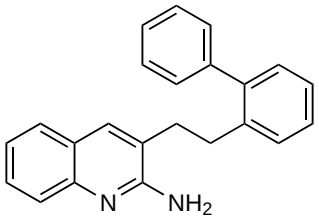
6.4.5 Exploration of synthetic pathway for 3-position extended 2-aminoquinolines

General Method 16: Synthesis of extended 2-aminoquinolines via *para*-methoxybenzyl amine substituted intermediate



A mixture of the 2-chloroquinoline derivative (1 eq) and 4-methoxybenzyl amine (10 eq) was heated at 140°C for 16 hr, cooled, and the excess reagent was removed by short-path distillation under reduced pressure or filtration through silica gel washing with dichloromethane. The residue was added to methanol (30 mL) or 1:1 methanol/ethanol (30 mL) with a catalytic amount of Pd-C catalyst (5%), and the mixture was stirred under a hydrogen atmosphere for 16 hr. The reaction mixture was filtered through Celite®, washing with methanol, and the solvent was removed by evaporation under reduced pressure. The residue was stirred in trifluoroacetic acid at 60°C for 1 hr, then cooled, diluted with dichloromethane (20 mL), and concentrated to dryness by evaporation under reduced pressure. The residue was again diluted with dichloromethane and concentrated to dryness by evaporation under reduced pressure, then diluted with saturated aqueous sodium bicarbonate solution (20 mL) and extracted with dichloromethane (3 x 25 mL). The organic extracts were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed by evaporation under reduced pressure. The crude residue was purified by column chromatography on silica gel with the specified eluant.

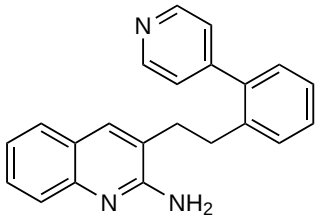
3-(2-((1,1'-Biphenyl)-2-yl)ethyl)quinolin-2-amine (138a)



Using General Method 16, **146a** (157 mg, 0.46 mmol) was reacted with 4-methoxybenzyl amine (1.2 mL, 9.2 mmol) for 16 hr. The excess reagent was removed by distillation under reduced pressure, and the residue was dissolved in methanol (30 mL) and reacted

under an atmosphere of hydrogen with a catalytic amount of Pd-C catalyst for 16 hr. The mixture was filtered through Celite® washing with methanol, and the volatile solvent was removed by evaporation under reduced pressure. The crude residue was treated with TFA (1.5 mL), and work-up followed by column chromatography on silica gel eluting with 1:19 methanol/dichloromethane yielded **138a** as a white solid (53 mg, 36%). MP: 173-176°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{23}H_{20}N_2$: 325.1705; found 325.1699. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.55-2.64 [2H, m, H(A)], 2.91-3.00 [2H, m, H(B)], 4.30 [2H, br s, NH_2], 7.21 [1H, td, $^3J_{5,6} = {}^3J_{6,7} = 7.4$ Hz, $^4J_{6,8} = 1.0$ Hz, H(6)], 7.24 [1H, br d‡, $^3J_{3',4'} = 7.1$ Hz, H(3')], 7.27-7.36 [5H, m, H(4') + H(5') + H(6') + H(2") + H(6")], 7.39 [1H, tt, $^3J_{3",4"} = {}^3J_{4",5"} = 7.4$ Hz, $^4J_{2",4"} = {}^3J_{4",6"} = 2.4$ Hz, H(4")], 7.41-7.46 [2H, m, H(3") + H(5")], 7.46-7.54 [3H, m, H(4) + H(5) + H(7)], 7.59 [1H, br d‡, $^3J_{7,8} = 8.4$ Hz, H(8)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 33.12 [C(B)], 33.80 [C(A)], 122.70 [C(6)], 123.00 [C(3)], 124.43 [C(4a)], 125.45 [br, C(8)], 126.61 [C(4')], 127.01 [C(5)], 127.35 [C(4")], 128.01 [C(5')], 128.67 [C(3") + C(5")], 129.11 [C(7)], 129.44 [C(2") + C(6")], 129.63 [C(6')], 130.41 [C(3')], 136.30 [br, C(4)], 138.63 [C(1')], 141.71 [C(1")], 142.01 [C(2')], 146.47 [br, C(8a)], 155.95 [C(2)].

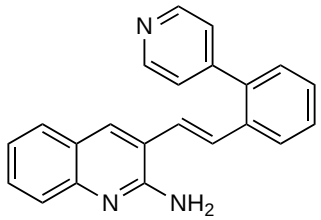
3-(2-(Pyridin-4-yl)phenethyl)quinolin-2-amine (139a)



Using General Method 16, **147a** (110 mg, 0.32 mmol) was reacted with 4-methoxybenzylamine (840 μL, 6.4 mmol) for 16 hr. The excess reagent was removed by distillation under reduced pressure, and the residue was dissolved in methanol (30 mL) and reacted under an atmosphere of hydrogen with a catalytic amount of Pd-C catalyst for 16 hr. The mixture was filtered through Celite® washing with methanol, and the volatile solvent was removed by evaporation under reduced pressure. The crude residue was treated with TFA (1 mL), and work-up followed by column chromatography on silica gel eluting with 1:19 methanol/dichloromethane yielded **139a** as a white solid (32 mg, 31%) and (*E*)-3-(2-(pyridin-2-yl)styryl)quinolin-2-amine (**161a**) as a white powder (6 mg, 6%).

*3-(2-(Pyridin-4-yl)phenethyl)quinolin-2-amine (**139a**):* MP: 165-167°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{19}N_3$: 326.1657; found 326.1653. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.63-2.72 [2H, m, H(A)], 2.96-3.05 [2H, m, H(B)], 4.45 [2H, br s, NH_2], 7.14-7.21 [3H, m, H(3') + H(2") + H(6")], 7.23 [1H, br t‡, $^3J_{5,6} = {}^3J_{6,7} = 7.4$ Hz, H(6)], 7.33 [1H, br td‡, $^3J_{3',4'} = {}^3J_{4',5'} = 7.1$ Hz, $^4J_{4',6'} = 1.9$ Hz, H(4')], 7.35-7.44 [3H, m, H(4) + H(5') + H(6')], 7.47-7.54 [2H, m, H(5) + H(7)], 7.62 [1H, d, $^3J_{7,8} = 8.3$ Hz, H(8)], 8.57-8.63 [2H, m, H(3")

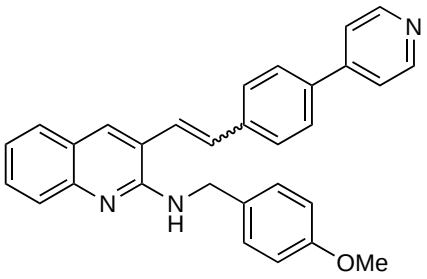
+ H(5")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.16 [C(B)], 33.48 [C(A)], 122.39 [C(3)], 122.94 [C(6)], 124.37 [C(2") + C(6")], 124.47 [C(4a)], 125.63 [C(8)], 126.91 [C(4')], 127.05 [C(5)], 129.00 [C(5')], 129.28 [C(7)], 129.85 [C(3') + C(6')], 136.28 [br, C(4)], 138.12 [C(1')], 139.41 [C(2')], 146.53 [br, C(8a)], 149.54 [C(1")], 149.98 [C(3") + C(5")], 155.88 [C(2)].



161a

(E)-*3-(2-(Pyridin-2-yl)styryl)quinolin-2-amine (**161a**):* HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{17}N_3$: 324.1501; found 324.1498. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.89 [2H, br s, NH_2], 7.05-7.11 [2H, m, H(A) + H(B)], 7.25 [1H, t, $^3J_{5,6} = {}^3J_{6,7} = 8.0$ Hz, H(6)], 7.33-7.38 [3H, m, H(3') + H(2") + H(6")], 7.44 [1H, br t‡, $^3J_{3',4'} = {}^3J_{4',5'} = 7.6$ Hz, H(4')], 7.49 [1H, br t‡, $^3J_{4',5'} = {}^3J_{5',6'} = 7.6$ Hz, H(5')], 7.53 [1H, br t‡, $^3J_{6,7} = {}^3J_{7,8} = 8.0$ Hz, H(7)], 7.60 [1H, br d‡, $^3J_{5,6} = 8.0$ Hz, H(5)], 7.64 [1H, br d‡, $^3J_{7,8} = 8.0$ Hz, H(8)], 7.78 [1H, br d‡, $^3J_{5',6'} = 7.6$ Hz, H(6')], 7.83 [1H, s, H(4)], 8.66-8.72 [2H, m, H(3") + H(5")]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 121.28 [C(3)], 123.31 [C(6)], 124.47 [C(4a)], 124.84 [br, C(2") + C(6")], 124.94 [C(A)], 125.89 [C(8)], 126.68 [C(6')], 127.72 [br, C(5)], 128.63 [C(4')], 129.09 [C(5')], 129.95 [C(7)], 130.15 [C(3')], 131.34 [C(B)], 134.42 [br, C(4)], 135.01 [C(1')], 138.60 [C(2')], 147.35 [br, C(8a)], 148.71 [C(1")], 149.98 [C(3") + C(5")], 155.19 [C(2)].

(*E*)-/(*Z*)-*N*-(4-Methoxybenzyl)-3-(4-(pyridin-4-yl)styryl)quinolin-2-amine (165c)

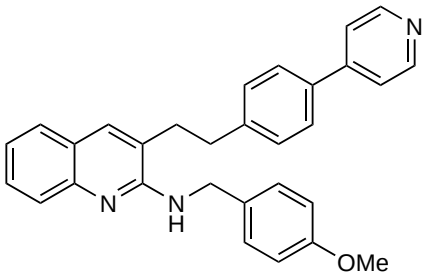


A mixture of **147c** (161 mg, 0.47 mmol) and 4-methoxybenzyl amine (1.23 mL, 9.4 mmol) was combined and stirred at 140°C for 16 hr. The mixture was purified by column chromatography on silica gel eluting with 1% methanol in dichloromethane to give a crude mixture of (*E*/*Z*)-**165c** as a yellow solid, which was used without further purification (152 mg, *73%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{30}H_{25}N_3O$: 444.2076; found 444.2067.

* contains residual 4-methoxybenzyl amine.

A sample of pure (*E*)-*N*-(4-methoxybenzyl)-3-(4-(pyridin-4-yl)styryl)quinolin-2-amine (*E*-**165c**) was obtained by recrystallisation from dichloromethane for the purposes of characterisation. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{30}H_{25}N_3O$: 444.2076; found 444.2067. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.80 [3H, s, OCH_3], 4.80 [2H, d, $^3J_{H,H} = 5.2$ Hz, CH_2], 4.96 [1H, br t, $^3J_{H,H} = 5.2$ Hz, NH], 6.87-6.92 [2H, m, H(3''') + H(5''')], 7.11 and 7.13 [2H, *AB*, *A*:d, *B*:d, $^3J_{A,B}(J_{AB}) = 16.0$ Hz, H(A) + H(B)], 7.24 [1H, ddd, $^3J_{5,6} = 8.0$ Hz, $^3J_{6,7} = 7.0$ Hz, $^4J_{6,8} = 1.1$ Hz, H(6)], 7.37-7.42 [2H, m, H(2''') + H(6''')], 7.49-7.57 [3H, m, H(7) + H(2'') + H(6'')], 7.58-7.68 [5H, m, H(5) + H(2') + H(3') + H(5') + H(6')], 7.76 [1H, br d, $^3J_{7,8} = 8.4$ Hz, H(8)], 7.95 [1H, s, H(4)], 8.64-8.69 [2H, m, H(3'') + H(5'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 45.52 [CH_2], 55.44 [OCH_3], 114.20 [C(3''') + C(5''')], 121.45 [C(2'') + C(6'')], 121.87 [C(3)], 122.66 [C(6)], 123.85 [C(A)], 123.92 [C(4a)], 126.49 [C(8)], 127.50 [C(3') + C(5')], 127.58 [C(2') + C(6')], 129.60 [C(7)], 129.72 [C(2''') + C(6''')], 131.90 [C(1''')], 132.86 [C(B)], 133.94 [C(4)], 137.77 [C(1')], 137.86 [C(4')], 147.66 [C(1'')], 147.86 [C(8a)], 150.51 [C(3'') + C(5'')], 154.42 [C(2)], 159.11 [C(4''')].

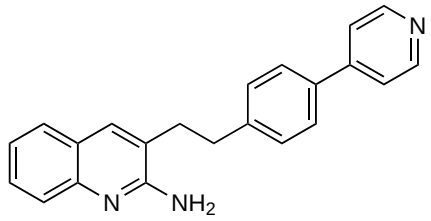
N-(4-Methoxybenzyl)-3-(4-(pyridin-4-yl)phenethyl)quinolin-2-amine (170c)



A solution of (*E*/*Z*)-**165c** (147 mg, 0.33 mmol) in methanol/ethanol (1:1, 40 mL) was heated at 40°C with a catalytic amount of 5% Pd-C catalyst under an atmosphere of hydrogen for 16 hr. The mixture was filtered through Celite® washing with methanol, and the solvent was removed by evaporation under reduced pressure to give **170c** which was used without further purification (102 mg, *69%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{30}H_{27}N_3O$: 446.2232; found 446.2234. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.80-2.87 [2H, m, H(A)], 3.04-3.11 [2H, m, H(B)], 3.78 [3H, s, OCH_3], 4.69 [1H, br t, $^3J_{H,H} = 4.7$ Hz, NH], 4.74 [2H, d, $^3J_{H,H} = 4.7$ Hz, NCH_2], 6.84-6.89 [2H, m, H(3''') + H(5''')], 7.22 [1H, ddd, $^3J_{5,6} = 8.0$ Hz, $^3J_{6,7} = 7.0$ Hz, $^4J_{6,8} = 1.1$ Hz, H(6)], 7.24-7.28 [2H, m, H(2') + H(6')], 7.30-7.35 [2H, m, H(2''') + H(6''')], 7.45-7.48 [2H, m, H(2'') + H(6'')], 7.49-7.57 [4H, m, H(5) + H(7) + H(3') + H(5')], 7.62 [1H, br s‡, H(4)], 7.77 [1H, br d‡, $^3J_{7,8} = 8.3$ Hz, H(8)], 8.62-8.66 [2H, m, H(3'') + H(5'')].

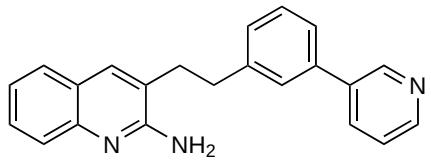
* contained residual 4-methoxybenzyl amine

3-(4-(Pyridin-4-yl)phenethyl)quinolin-2-amine (139c)



A mixture of **170c** (89 mg, 0.20 mmol) and trifluoroacetic acid (1 mL) was heated at 60°C for 1 hr. The mixture was then cooled and diluted with dichloromethane (20 mL), and concentrated to dryness by evaporation under reduced pressure. The residue was re-suspended in dichloromethane and concentrated to dryness by evaporation under reduced pressure, then diluted with saturated aqueous sodium bicarbonate solution (20 mL) and extracted with dichloromethane (3 x 25 mL). The organic extracts were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed by evaporation under reduced pressure. The residue was purified by column chromatography on silica gel eluting with 5% methanol in dichloromethane, to give **139c** as a white solid (42 mg, 65%). MP: 212-216°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{19}N_3$: 326.1657; found 326.1651. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.91-2.98 [2H, m, H(A)], 3.09-3.16 [2H, m, H(B)], 4.99 [2H, br s, NH_2], 7.28 [1H, br t, $^3J_{5,6} = {}^3J_{6,7} = 7.5$ Hz, H(6)], 7.32-7.35 [2H, m, H(2') + H(6')], 7.48-7.51 [2H, m, H(2") + H(6")], 7.54-7.62 [4H, m, H(5) + H(7) + H(3') + H(5')], 7.68-7.72 [2H, m, H(4) + H(8)], 8.63-8.68 [2H, m, H(3") + H(5")].

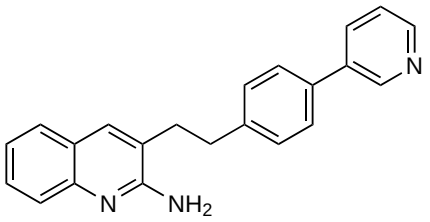
3-(3-(Pyridin-3-yl)phenethyl)quinolin-2-amine (140b)



Using General Method 16, **148b** (124 mg, 0.36 mmol) was reacted with 4-methoxybenzylamine (945 μL, 7.2 mmol) for 16 hr. The excess reagent was removed by distillation under reduced pressure, and the residue was dissolved in methanol (30 mL) and reacted under an atmosphere of hydrogen with a catalytic amount of Pd-C catalyst for 16 hr. The mixture was filtered through Celite® washing with methanol, and the volatile solvent was removed by evaporation under reduced pressure. The crude residue was treated with TFA (1.5 mL), and work-up followed by column chromatography on silica gel eluting with 1:19 methanol/dichloromethane yielded **140b** as a pale yellow solid (36 mg, 31%). MP: 172-176°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{19}N_3$: 326.1657; found 326.1653. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.91-3.00 [2H, m, H(A)], 3.09-3.19 [2H, m, H(B)], 5.43 [2H, br s, NH_2], 7.22-7.29 [2H, m, H(6) +

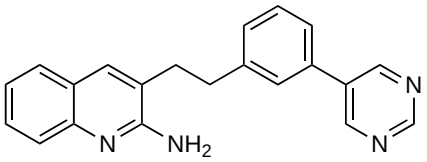
H(6')], 7.32 [1H, dd, $^{3}J_{5'',6''}$ = 7.9 Hz, $^{3}J_{4'',5''}$ = 4.8 Hz, H(5'')], 7.37 [1H, br s, H(2')], 7.39-7.47 [2H, m, H(4') + H(5')], 7.51-7.61 [2H, m, H(5) + H(7)], 7.66-7.73 [2H, m, H(4) + H(8)], 7.76 [1H, br d‡, $^{3}J_{5'',6''}$ = 7.9 Hz, H(6'')], 8.57 [1H, dd, $^{3}J_{4'',5''}$ = 4.8 Hz, $^{4}J_{4'',6''}$ = 1.0 Hz, 8.79 [1H, d, $^{4}J_{2'',6''}$ = 2.0 Hz, H(2'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 33.06 [C(A)], 34.45 [C(B)], 122.81 [C(3)], 123.29 [C(6)], 123.65 [C(5'')], 124.05 [C(4a)], 124.66 [br, C(8)], 125.48 [C(4')], 127.19 [C(5)], 127.49 [C(2')], 128.28 [C(6')], 129.54 [C(5')], 129.67 [C(7)], 134.50 [C(6'')], 136.60 [C(1'')], 136.69 [C(4)], 138.41 [C(3')], 141.71 [C(1')], 145.12 [br, C(8a)], 148.43 [C(2'')], 148.69 [C(4'')], 155.93 [C(2)].

3-(4-(Pyridin-3-yl)phenethyl)quinolin-2-amine (140c)



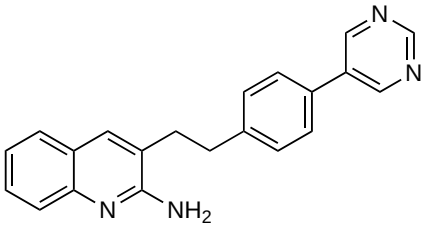
Using General Method 16, **148c** (129 mg, 0.38 mmol) was reacted with 4-methoxybenzylamine (980 μL, 7.5 mmol) for 16 hr. The excess reagent was removed by distillation under reduced pressure, and the residue was dissolved in methanol (30 mL) and reacted under an atmosphere of hydrogen with a catalytic amount of Pd-C catalyst for 16 hr. The mixture was filtered through Celite® washing with methanol, and the volatile solvent was removed by evaporation under reduced pressure. The crude residue was treated with TFA (1.5 mL), and work-up followed by column chromatography on silica gel eluting with 1:19 methanol/dichloromethane yielded **140c** as a pale yellow solid (22 mg, 18%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{22}H_{19}N_3$: 326.1657; found 326.1658. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.89-3.02 [2H, m, H(A)], 3.08-3.18 [2H, m, H(B)], 5.07 [2H, br s, NH_2], 7.27 [1H, t, $^{3}J_{5,6}$ = $^{3}J_{6,7}$ = 7.7 Hz, H(6)], 7.30-7.40 [3H, m, H(2') + H(6') + H(5'')], 7.49-7.57 [3H, m, H(7) + H(3') + H(5')], 7.59 [1H, d, $^{3}J_{5,6}$ = 7.7 Hz, H(5)], 7.66-7.73 [2H, m, H(4) + H(8)], 7.86 [1H, br d‡, $^{3}J_{5'',6''}$ = 7.9 Hz, H(6'')], 8.59 [1H, br d‡, $^{3}J_{4'',5''}$ = 4.6 Hz, H(4'')], 8.84 [1H, br s‡, H(2'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 33.09 [C(A)], 34.17 [C(B)], 122.77 [C(3)], 123.15 [C(6)], 123.69 [C(5'')], 124.32 [C(4a)], 125.19 [C(8)], 127.20 [C(5)], 127.52 [C(3') + C(5')], 129.34 [C(2') + C(6')], 129.48 [C(7)], 134.31 [C(6'')], 136.18 [C(4')], 136.37 [br, C(4) + C(1'')], 140.98 [C(1')], 145.79 [br, C(8a)], 148.39 [C(2'')], 148.59 [C(4'')], 156.01 [C(2)].

3-(3-(Pyrimidin-5-yl)phenethyl)quinolin-2-amine (141b)



Using General Method 16, **149b** (116 mg, 0.34 mmol) was reacted with 4-methoxybenzylamine (880 μL, 6.7 mmol) for 16 hr. The excess reagent was removed by distillation under reduced pressure, and the residue was dissolved in methanol (30 mL) and reacted under an atmosphere of hydrogen with a catalytic amount of Pd-C catalyst for 16 hr. The mixture was filtered through Celite® washing with methanol, and the volatile solvent was removed by evaporation under reduced pressure. The crude residue was treated with TFA (1.5 mL), and work-up followed by column chromatography on silica gel eluting with 1:19 methanol/dichloromethane yielded **141b** as a pale yellow solid (34 mg, 31%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{18}N_4$: 327.1610; found 327.1590. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.92-2.99 [2H, m, H(A)], 3.12-3.19 [2H, m, H(B)], 4.88 [2H, br s, NH_2], 7.26 [1H, td, $^3J_{5,6} = {}^3J_{6,7} = 7.4$ Hz, $^4J_{6,8} = 0.9$ Hz, H(6)], 7.33 [1H, br d‡, $^3J_{5',6'} = 7.1$ Hz, H(6')], 7.37 [1H, br s, H(2')], 7.41-7.50 [2H, m, H(4') + H(5')], 7.51-7.60 [2H, m, H(5) + H(7)], 7.64-7.70 [2H, m, H(4) + H(8)], 8.87 [2H, s, H(2'') + H(6'')], 9.20 [1H, s, H(4'')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 33.28 [C(A)], 34.49 [C(B)], 122.39 [C(3)], 123.05 [C(6)], 124.47 [C(4a)], 125.31 [C(4')], 125.70 [C(8)], 127.10 [C(5)], 127.34 [C(2')], 129.22 [C(6')], 129.38 [C(7)], 129.90 [C(5')], 134.39 [C(1'')], 134.84 [C(3')], 136.17 [C(4)], 142.37 [C(1')], 146.55 [br, C(8a)], 155.06 [C(2'') + C(6'')], 156.04 [C(2)], 157.71 [C(4'')].

3-(4-(Pyrimidin-5-yl)phenethyl)quinolin-2-amine (141c)

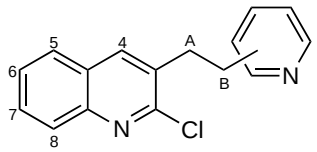


Using General Method 16, **149c** (132 mg, 0.38 mmol) was reacted with 4-methoxybenzylamine (1.0 mL, 7.7 mmol) for 16 hr. The excess reagent was removed by distillation under reduced pressure, and the residue was dissolved in methanol (30 mL) and reacted under an atmosphere of hydrogen with a catalytic amount of Pd-C catalyst for 16 hr. The mixture was filtered through Celite® washing with methanol, and the volatile solvent was removed by evaporation under reduced pressure. The crude residue was treated with TFA (1.5 mL), and work-up followed by column chromatography on silica gel eluting with 1:19 methanol/dichloromethane

yielded **141c** as a pale yellow solid (40 mg, 32%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{21}H_{18}N_4$: 327.1610; found 327.1591. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.91-2.99 [2H, m, H(A)], 3.10-3.18 [2H, m, H(B)], 4.88 [2H, br s, NH_2], 7.26 [1H, ddd, $^3J_{5,6} = 8.0$ Hz, $^3J_{6,7} = 7.4$ Hz, $^4J_{6,8} = 0.9$ Hz, H(6)], 7.35-7.39 [2H, m, H(2') + H(6')], 7.49-7.60 [4H, m, H(5) + H(7) + H(3') + H(5')], 7.66-7.70 [2H, m, H(4) + H(8)], 8.94 [2H, s, H(2") + H(6")], 9.20 [1H, s, H(4")].

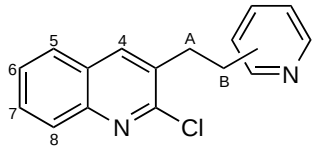
6.4.6 Synthesis of 3-position pyridinylethyl-extended 2-aminoquinoline derivatives

General Method 17: Synthesis of 3-position pyridinylvinyl substituted 2-chloroquinoline derivatives via Wittig reaction with LiHMDS



A suspension of triphenyl(pyridinylmethyl)phosphonium bromide derivative **52** (1.5 eq) in anhydrous THF was stirred and cooled to 0°C under an atmosphere of nitrogen. LiHMDS solution (1.0 M in THF, 2.0 eq) was added dropwise and the mixture was stirred for 10 minutes. A solution of **144** (1.0 eq) in anhydrous THF was added and the mixture was stirred at 30 minutes for 0°C then at room temperature for 3 hr or until complete. The reaction mixture was quenched with water (20 mL) then extracted with DCM (2 x 25 mL). The organic extracts were dried over $MgSO_4$, filtered, and solvent removed by evaporation under reduced pressure. A solution of 2:3 ethyl acetate/hexane was added to the crude residue and the mixture was filtered to remove insoluble solid impurities. The filtrate was concentrated by evaporation under reduced pressure and the residue purified by flash column chromatography on silica gel with the specified eluant.

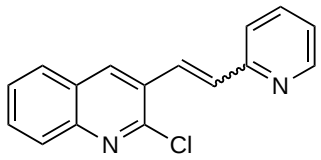
General Method 18: Synthesis of 3-position pyridinylvinyl substituted 2-chloroquinoline derivatives via Wittig reaction with sodium *tert*-butoxide



Sodium *tert*-butoxide (1.4 eq) was added to suspension of triphenylphosphonium halide Wittig reagent (2.4 eq) stirred in anhydrous DMF (6 mL) under an atmosphere of nitrogen, and the reaction mixture was stirred for 20 min. A solution of quinoline **144** (1 eq) in anhydrous DMF was added and the mixture was stirred for 4 hr or until complete, and quenched with

methanol. The mixture was concentrated to dryness by evaporation under reduced pressure, then suspended in ethyl acetate/hexane (2:3, 40 mL) and filtered to remove insoluble solid impurities. The filtrate was concentrated to dryness by evaporation under reduced pressure and the residue was purified by flash column chromatography on silica gel with the specified eluant.

2-Chloro-3-(2-(pyridin-2-yl)vinyl)quinoline (172a)

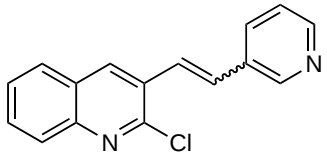


Synthesis method a. Using General Method 17, **52a** (0.68 g, 1.6 mmol), **144** (200 mg, 1.0 mmol), and LiHMDS solution (1.0M in THF, 2.09 mL, 2.1 mmol) were reacted in THF (10 mL). The crude residue was purified by column chromatography on silica gel eluting with 1% methanol in dichloromethane to give **172a** as a brown oil (144 mg, 52%). R_f = 0.25 (2% methanol in dichloromethane).

A sample of (*E*)-2-chloro-3-(2-(pyridin-2-yl)vinyl)quinoline (*E*-**172a**) was isolated by column chromatography for the purposes of characterisation. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{11}{}^{35}ClN_2/C_{16}H_{11}{}^{37}ClN_2$: 267.0689/269.0660; found 267.0684/269.0659. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 [1H, dd, $^3J_{4',5'}$ = 7.4 Hz, $^3J_{3',4'}$ = 4.8 Hz, H(4')], 7.28 [1H, d, $^3J_{A,B}$ = 16.1 Hz, H(B)], 7.49 [1H, d, $^3J_{5',6'}$ = 7.8 Hz, H(6')], 7.56 [1H, t, $^3J_{5,6}$ = $^3J_{6,7}$ = 8.0 Hz, H(6)], 7.68-7.73 [2H, m, H(7) + H(5')], 7.84 [1H, d, $^3J_{5,6}$ = 8.0 Hz, H(5)], 8.00 [1H, d, $^3J_{7,8}$ = 9.0 Hz, H(8)], 8.03 [1H, d, $^3J_{A,B}$ = 16.1 Hz, H(A)], 8.42 [1H, s, H(4)], 8.66 [1H, d, $^3J_{3'/4'}$ = 4.8 Hz, H(3')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 122.43 [C(6')], 122.94 [C(4')], 127.45 [C(6)], 127.52 [C(4a)], 127.65 [C(A)], 127.82 [C(5)], 128.44 [C(8)], 129.87 [C(3)], 130.65 [C(7)], 132.77 [C(B)], 134.58 [C(4)], 136.76 [C(5')], 147.23 [C(8a)], 150.06 [C(3')], 150.47 [C(2)], 154.93 [C(1')].

Synthesis method b. Using General Method 17, **52a** (254 mg, 0.58 mmol), **144** (80 mg, 0.42 mmol), and sodium *tert*-butoxide (96 mg, 1.0 mmol) in DMF (7 mL). The crude residue was purified by column chromatography on silica gel eluting with 1% methanol in dichloromethane to give *E*-**172a** as a brown oil (90 mg, 81%). Data as above.

2-Chloro-3-(2-(pyridin-3-yl)vinyl)quinoline (172b)

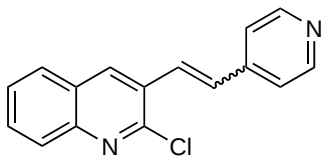


Synthesis method a. Using General Method 17, **52b** (0.85 g, 2.2 mmol), **144** (250 mg, 1.3 mmol), and LiHMDS solution (1.0M in THF, 3.1 mL, 3.1 mmol) were reacted in THF (10 mL). The crude residue was purified by column chromatography on silica gel eluting with 1% methanol in dichloromethane to give **172b** as a brown oil (115 mg, 33%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{11}{}^{35}ClN_2/C_{16}H_{11}{}^{37}ClN_2$: 267.0689/269.0660; found 267.0686/269.0660.

A sample of (*Z*)-2-chloro-3-(2-(pyridin-3-yl)vinyl)quinoline (*Z*-**172b**) was isolated by column chromatography for the purposes of characterisation. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{11}{}^{35}ClN_2/C_{16}H_{11}{}^{37}ClN_2$: 267.0689/269.0660; found 267.0684/269.0659. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.83 [1H, d, $^3J_{A,B}$ = 12.1 Hz, H(B)], 6.89 [1H, dd, $^3J_{A,B}$ = 12.1 Hz, $^4J_{4,A}$ = 0.6 Hz, H(A)], 7.08 [1H, dd, $^3J_{5',6'}$ = 7.9 Hz, $^3J_{4',5'}$ = 4.8 Hz, H(5')], 7.44 [1H, dt, $^3J_{5',6'}$ = 7.9 Hz, $^4J_{2',6'}$ = $^4J_{4',6'}$ = 1.8 Hz, H(6')], 7.48 [1H, ddd, $^3J_{5,6}$ = 8.1 Hz, $^3J_{6,7}$ = 6.9 Hz, $^4J_{6,8}$ = 1.0 Hz, H(6)], 7.56 [1H, dd, $^3J_{5,6}$ = 8.1 Hz, $^4J_{5,7}$ = 1.2 Hz, H(5)], 7.69 [1H, ddd, $^3J_{7,8}$ = 8.5 Hz, $^3J_{6,7}$ = 6.9 Hz, $^4J_{5,7}$ = 1.2 Hz, H(7)], 7.89 [1H, br s‡, H(4)], 8.00 [1H, br d‡, $^3J_{7,8}$ = 8.5 Hz, H(8)], 8.41 [1H, dd, $^3J_{4',5'}$ = 4.8 Hz, $^4J_{4',6'}$ = 1.8 Hz, H(4')], 8.47 [1H, d, $^4J_{2',6'}$ = 1.8 Hz, H(2')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 123.28 [C(5')], 126.92 [C(4a)], 127.30 [C(6)], 127.55 [C(5)], 128.04 [C(A)], 128.33 [C(8)], 129.36 [C(3)], 129.70 [C(B)], 130.72 [C(7)], 131.76 [C(1')], 135.79 [C(6')], 138.30 [C(4)], 147.06 [C(8a)], 148.66 [C(4')], 150.12 [C(2')], 150.26 [C(2)].

Synthesis method b. Using General Method 18, **52b** (228 mg, 0.58 mmol), **144** (80 mg, 0.42 mmol), and sodium *tert*-butoxide (96 mg, 1.0 mmol) were reacted in DMF (10 mL). The crude residue was purified by column chromatography on silica gel eluting with 1% methanol in dichloromethane to give **172b** as a brown oil (77 mg, 69%). R_f = 0.20 (2% methanol in dichloromethane). Data as above.

2-Chloro-3-(2-(pyridin-4-yl)vinyl)quinoline (172c)



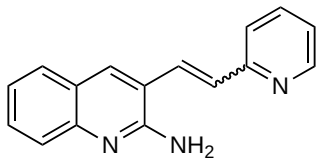
Synthesis method a. Using General Method 17, **52c** (0.47 g, 1.1 mmol), **144** (160 mg, 0.84

mmol), and LiHMDS solution (1.0 M in THF, 1.7 mL, 1.7 mmol) were reacted in THF (10 mL). The crude residue was purified by column chromatography on silica gel eluting with 2.5% methanol in dichloromethane to give **172c** as a brown oil (71 mg, 32%). $R_f = 0.12$ (2% methanol in dichloromethane). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{11}{}^{35}ClN_2/C_{16}H_{11}{}^{37}ClN_2$: 267.0689/269.0660; found 267.0685/269.0658. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.79 [0.8H, d, $^3J_{A,B} = 12.2$ Hz, H(B)], 6.95 [0.8H, d, $^3J_{A,B} = 12.2$ Hz, H(A)], 7.03-7.08 [1.6H, m, H(2') + H(6')], 7.12 [0.2H, d, $^3J_{*A,*B} = 16.2$ Hz, *H(B)], 7.43-7.45 [0.4H, m, *H(2') + *H(6')], 7.50 [0.8H, ddd, $^3J_{5,6} = 8.1$ Hz, $^3J_{6,7} = 7.0$ Hz, $^4J_{6,8} = 1.0$ Hz, H(6)], 7.54-7.61 [1H, m, H(5) + *H(6)], 7.68-7.76 [1.2H, m, H(7) + *H(7) + *H(A)], 7.84-7.89 [1H, m, H(4) + *H(5)], 7.99-8.04 [1H, m, H(8) + *H(8)], 8.41 [0.2H, s, *H(4)], 8.42-8.47 [1.6H, m, H(3') + H(5')], 8.63-8.67 [0.4H, m, *H(3') + *H(5')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 121.23 [*C(2') + *C(6')], 123.40 [C(2') + C(6')], 126.87 [C(4a)], 127.42 [C(5)], 127.44 [C(6)], 127.64 [C(5)], 127.81 [*C(5)], 128.15 [*C(A)], 128.41 [C(8)], 128.51 [*C(8)], 128.54 [*C(4a)], 128.99 [C(3)], 129.28 [*C(3)], 129.46 [C(A)], 130.61 [*C(B)], 130.84 [C(B)], 130.92 [C(7)], 130.94 [*C(7)], 134.72 [*C(4)], 138.50 [C(4)], 143.61 [C(1')], 143.78 [*C(1')], 147.23 [C(8a)], 147.37 [*C(8a)], 150.08 [*C(2)], 150.11 [C(2)], 150.26 [C(3') + C(5')], 150.55 [*C(3') + *C(5')].

* denotes signals corresponding to the minor *E*-isomer.

Synthesis method b. Using General Method 18, **52c** (254 mg, 0.58 mmol), **144** (80 mg, 0.42 mmol), and sodium *tert*-butoxide (96 mg, 1.0 mmol) were reacted in DMF (10 mL). The crude residue was purified by column chromatography on silica gel eluting with dichloromethane/ methanol (99:1) to give **172c** as a brown oil (50 mg, 45%). Data as above.

3-(2-(Pyridin-2-yl)vinyl)quinolin-2-amine (173a)

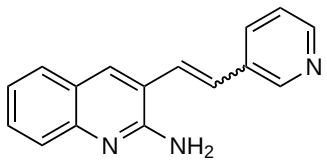


Using General Method 11, **172a** (134 mg, 0.50 mmol), $Pd(dba)_2$ (2.9 mg, 5.0 μmol), DavePhos (2.4 mg, 6.1 μmol), and LiHMDS solution (1.0M in THF, 1.10 mL, 1.1 mmol) were reacted in 1,4-dioxane (2.5 mL) for 16 hr. Work-up as specified and flash column chromatography on silica gel eluting with 1:19 methanol/dichloromethane gave **173a** as a pale yellow solid (15 mg, 12%).

A sample of (*E*)-3-(2-(pyridin-2-yl)vinyl)quinolin-2-amine (*E*-**173a**) was isolated by column chromatography for the purposes of characterisation. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.15 [2H, br s, NH_2], 7.16-7.23 [2H, m, H(B) + H(4')], 7.27 [1H, td, $^3J_{5,6} = {}^3J_{6,7} = 7.5$ Hz, $^4J_{6,8} = 0.8$ Hz, H(6)], 7.36 [1H, br d‡, $^3J_{5',6'} = 7.8$ Hz, H(6')], 7.55 [1H, ddd, $^3J_{7,8} = 8.4$ Hz, $^3J_{6,7}$

= 7.5 Hz, $^4J_{5,7}$ = 1.3 Hz, H(7)], 7.64-7.72 [3H, m, H(5) + H(8) + H(5')], 7.76 [1H, d, $^3J_{A,B}$ = 15.7 Hz, H(A)], 8.09 [1H, s, H(4)], 8.62 [1H, br d‡, $^3J_{3',4'}$ = 4.6 Hz, H(3')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 120.78 [C(3)], 122.80 [C(4')], 122.91 [C(6')], 123.13 [C(6)], 124.41 [C(4a)], 125.83 [C(8)], 126.98 [C(A)], 127.78 [C(5)], 130.02 [C(7)], 131.95 [C(B)], 134.77 [C(4)], 136.90 [C(5')], 147.57 [C(8a)], 149.93 [C(3')], 154.91 [C(1')], 155.54 [C(2)].

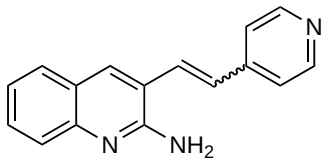
3-(2-(Pyridin-3-yl)vinyl)quinolin-2-amine (173b)



Using General Method 11, **172b** (110 mg, 0.41 mmol), $Pd(dba)_2$ (2.4 mg, 4.1 μmol), DavePhos (1.9 mg, 4.9 μmol), and LiHMDS solution (1.0M in THF, 0.91 mL, 0.91 mmol) were reacted in 1,4-dioxane (2.5 mL) for 16 hr. Work-up as specified and flash column chromatography on silica gel eluting with 1:19 methanol/dichloromethane gave **173b** as a pale yellow solid (14 mg, 14%). R_f = 0.38 (1:9 methanol/dichloromethane).

A sample of pure (*Z*)-3-(2-(pyridin-3-yl)vinyl)quinolin-2-amine (*Z*-**173b**) was isolated by column chromatography for the purposes of characterisation. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{13}N_3$: 248.1188; found 248.1184. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.02 [2H, br s, NH_2], 6.68 [1H, dd, $^3J_{A,B}$ = 12.1 Hz, $^4J_{A,4}$ = 0.8 Hz, H(A)], 6.80 [1H, d, $^3J_{A,B}$ = 12.1 Hz, H(B)], 7.06 [1H, dd, $^3J_{5',6'}$ = 8.0 Hz, $^3J_{4',5'}$ = 4.8 Hz, H(5')], 7.23 [1H, ddd, $^3J_{5,6}$ = 8.0 Hz, $^3J_{6,7}$ = 7.0 Hz, $^4J_{6,8}$ = 1.1 Hz, H(6)], 7.46 [1H, dt, $^3J_{5',6'}$ = 8.0 Hz, $^4J_{2',6'}$ = $^4J_{4',6'}$ = 1.8 Hz, H(6')], 7.50 [1H, br d‡, $^3J_{5,6}$ = 8.0 Hz, H(5)], 7.55 [1H, ddd, $^3J_{7,8}$ = 8.4 Hz, $^3J_{6,7}$ = 7.0 Hz, $^4J_{5,7}$ = 1.4 Hz, H(7)], 7.67 [1H, br d‡, $^3J_{7,8}$ = 8.4 Hz, H(8)], 7.71 [1H, br s‡, H(4)], 8.41 [1H, dd, $^3J_{4',5'}$ = 4.8 Hz, $^4J_{4',6'}$ = 1.8 Hz, H(4')], 8.50 [1H, d, $^4J_{4',6'}$ = 1.8 Hz, H(2')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 119.91 [C(3)], 123.07 [C(6)], 123.37 [C(5')], 123.79 [C(4a)], 125.74 [C(8)], 126.87 [C(A)], 127.63 [C(5)], 130.10 [C(7)], 130.85 [C(B)], 131.72 [C(1')], 135.33 [C(6')], 137.01 [C(4)], 147.26 [C(8a)], 149.08 [C(4')], 150.46 [C(2')], 154.79 [C(2)].

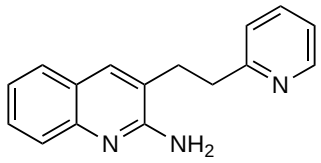
3-(2-(Pyridin-4-yl)vinyl)quinolin-2-amine (173c)



Using General Method 11, **172c** (60 mg, 0.22 mmol), $Pd(dba)_2$ (1.3 mg, 2.2 μmol), DavePhos (1.1 mg, 2.7 μmol), and LiHMDS solution (1.0M in THF, 0.49 mL, 0.49 mmol) were reacted in 1,4-dioxane (2.5 mL) for 16 hr. Work up as specified gave a crude mixture which could

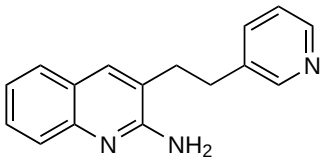
not be purified. ^{1}H NMR analysis of the crude mixture did not indicate signals corresponding to the desired product or recovered reagent.

3-(2-(Pyridin-2-yl)ethyl)quinolin-2-amine (142a)



Using General Method 3, **173a** (11 mg, 0.04 mmol) was combined in methanol (40 mL) with a catalytic amount of 5% Pd-C catalyst and stirred for 16 hr under an atmosphere of hydrogen. Work-up as specified and column chromatography on silica gel eluting with 2% methanol in dichloromethane gave **142a** as a yellow oil (11 mg, 97%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{15}N_3$: 250.1344; found 250.1341. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.05-3.12 [2H, m, H(A)], 3.12-3.20 [2H, m, H(B)], 5.61 [2H, br s, NH_2], 7.12 [1H, d, $^3J_{5',6'} = 7.8$ Hz, H(6')], 7.15 [1H, dd, $^3J_{4',5'} = 7.5$ Hz, $^3J_{3',4'} = 4.9$ Hz, H(4')], 7.24 [1H, td, $^3J_{5,6} = {}^3J_{6,7} = 7.2$ Hz, $^4J_{6,8} = 0.9$ Hz, H(6)], 7.51 [1H, ddd, $^3J_{7,8} = 8.4$ Hz, $^3J_{6,7} = 7.2$ Hz, $^3J_{5,7} = 1.3$ Hz, H(7)], 7.55-7.61 [2H, m, H(5) + H(5')], 7.66 [1H, br d‡, $^3J_{7,8} = 8.4$ Hz, H(8)], 7.71 [1H, s, H(4)], 8.59 [1H, br d‡, $^3J_{3',4'} = 4.9$ Hz, H(3')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.11 [C(A)], 37.00 [C(B)], 121.73 [C(4')], 122.75 [C(6)], 123.25 [C(6')], 123.59 [C(3)], 124.20 [C(4a)], 125.09 [br, C(8)], 127.09 [C(5)], 129.24 [C(7)], 136.33 [C(4)], 136.79 [C(5')], 146.06 [br, C(8a)], 149.59 [C(3')], 156.46 [C(2)], 160.61 [C(1')].

3-(2-(Pyridin-3-yl)ethyl)quinolin-2-amine (142b)

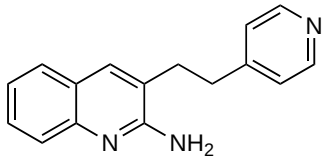


Synthesis method a. Using General Method 3, **173b** (12 mg, 0.05 mmol) was combined in methanol (40 mL) with a catalytic amount of 5% Pd-C catalyst and stirred for 16 hr under an atmosphere of hydrogen. Work-up as specified and column chromatography on silica gel eluting with 1% methanol in dichloromethane gave **142b** as a yellow oil (6 mg, 50%). MP: 179-182°C. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{16}H_{15}N_3$: 250.1344; found 250.1341. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.84-2.96 [2H, m, H(A)], 3.01-3.13 [2H, m, H(B)], 4.85 [2H, br s, NH_2], 7.21 [1H, dd, $^3J_{5',6'} = 7.5$ Hz, $^3J_{4',5'} = 4.9$ Hz, H(5')], 7.26 [1H, t, $^3J_{5,6} = {}^3J_{6,7} = 7.4$ Hz, H(6)], 7.47 [1H, br d, $^3J_{5',6'} = 7.5$ Hz, H(6')], 7.50-7.60 [2H, m, H(5) + H(7)], 7.63 [1H, s, H(4)], 7.67 [1H, d, $^3J_{7,8} = 8.4$ Hz, H(8)], 8.45-8.58 [2H, m, H(2') + H(4')]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.54 [C(B)], 32.98 [C(A)], 121.99 [C(3)], 123.01 [C(6)], 123.55

[C(5')], 124.45 [C(4a)], 125.77 [C(8)], 127.15 [C(5)], 129.34 [C(7)], 136.06 [C(6')], 136.13 [C(4)], 136.22 [C(1')], 146.70 [C(8a)], 148.10 [C(4')], 150.02 [C(2')], 155.94 [C(2)].

Synthesis method b. Using General Method 16, a mixture of (*E*/*Z*)-**172b** (55 mg, 0.21 mmol) was treated with 4-methoxybenzylamine (0.54 mL, 4.1 mmol) for 16 hr then cooled and chromatographed through silica gel eluting with dichloromethane. The fractions containing no excess reagent were reacted under an atmosphere of hydrogen with a catalytic amount of 5% Pd-C catalyst in methanol (20 mL) and then treated with TFA (1 mL). Work-up and purification by column chromatography on silica gel eluting with 1% methanol in dichloromethane gave **142b** as a yellow solid (17 mg, 33%). Data as above.

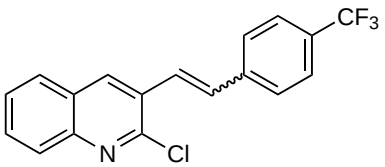
3-(2-(Pyridin-4-yl)ethyl)quinolin-2-amine (142c)



Using General Method 16, a mixture of (*E*/*Z*)-**172c** (62 mg, 0.23 mmol) was treated with 4-methoxybenzylamine (0.61 mL, 4.6 mmol) for 16 hr then cooled and chromatographed through silica gel eluting with dichloromethane, to give a crude brown mixture which could not be further purified (16 mg). ^{1}H NMR analysis of the crude mixture was used to identify signals corresponding to the desired product, however due to low recovery the subsequent steps were not attempted.

6.4.7 Synthesis of simple 3-position phenethyl-extended 2-aminoquinoline derivatives

2-Chloro-3-(4-(trifluoromethyl)styryl)quinoline (176a)

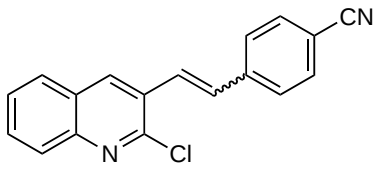


Using General Method 15, **36p** (161 mg, 0.54 mmol), **144** (80 mg, 0.42 mmol), and sodium *tert*-butoxide (96 mg, 1.0 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed by column chromatography eluting with dichloromethane gave **176a** as a white solid (139 mg, 100%). A sample of pure *E*-isomer was isolated by chromatography for the purposes of characterisation. HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{11}{}^{35}ClF_3N/C_{16}H_{11}{}^{37}ClF_3N$: 334.0610/336.0581; found 334.0606/336.0581. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 [1H, d,

$^3J_{A,B}$ = 16.2 Hz, H(B)], 7.54-7.63 [2H, m, H(6) + H(A)], 7.63-7.70 [4H, m, H(2') + H(3') + H(5') + H(6')], 7.72 [1H, ddd, $^3J_{7,8}$ = 8.4 Hz, $^3J_{6,7}$ = 7.0 Hz, $^4J_{5,7}$ = 1.3 Hz, H(7)], 7.85 [1H, br d‡, $^3J_{5,6}$ = 8.1 Hz, H(5)], 8.01 [1H, d, $^3J_{7,8}$ = 8.4 Hz, H(8)], 8.39 [1H, s, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 124.22 [q, $^1J_{C,F}$ = 272.1 Hz, CF_3], 125.96 [q, $^3J_{C,F}$ = 3.8 Hz, C(3') + C(5')], 126.23 [C(A)], 127.23 [C(2') + C(6')], 127.55 [C(4a)], 127.59 [C(6)], 127.77 [C(5)], 128.53 [C(8)], 129.79 [C(3)], 130.34 [q, $^2J_{C,F}$ = 32.4 Hz, C(4')], 130.74 [C(7)], 131.73 [C(B)], 134.32 [C(4)], 140.09 [q, $^5J_{C,F}$ = 1.4 Hz, C(1')], 147.24 [C(8a)], 150.22 [C(2)].

This data is consistent with that reported in literature.[136]

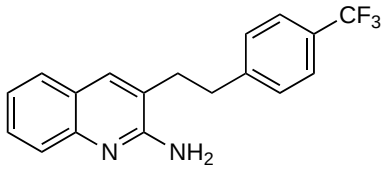
4-(2-(2-Chloroquinolin-3-yl)vinyl)benzonitrile (176b)



Using General Method 15, **36s** (370 mg, 1.46 mmol), **144** (200 mg, 1.04 mmol), and sodium *tert*-butoxide (241 mg, 2.51 mmol) were reacted in DMF (6 mL) for 4 hr. Work-up followed by column chromatography eluting with dichloromethane gave **176b** as a white solid (208 mg, 69%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{11}{}^{35}ClF_3N/C_{16}H_{11}{}^{37}ClF_3N$: 291.0689/293.0660; found 291.0685/293.0661. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 [0.1H, d, $^3J_{*A,*B}$ = 12.2 Hz, *H(B)], 6.91 [0.1H, d, $^3J_{*A,*B}$ = 12.2 Hz, *H(A)], 7.19 [0.9H, d, $^3J_{A,B}$ = 16.2 Hz, H(B)], 7.25-7.29 [0.2H, m, *H(2') + *H(6')], 7.45-7.53 [0.3H, m, *H(6) + *H(3') + *H(5')], 7.55-7.61 [1H, m, H(6) + *H(5)], 7.61-7.77 [5.6H, m, H(A) + H(7) + H(2') + H(3') + H(5') + H(6') + *H(7) + *H(8)], 7.83-7.88 [1H, m, H(5) + *H(4)], 8.01 [0.9H, d, $^3J_{7,8}$ = 8.5 Hz, H(8)], 8.40 [0.9H, s, H(4)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 111.33 [C(4')], 111.78 [*C(4')], 118.70 [*CN], 118.87 [CN], 126.91 [*C(4a)], 127.33 [C(A)], 127.44-127.56 [m, C(4a) + C(2') + C(6') + *C(6)], 127.61 [*C(5)], 127.67 [C(6)], 127.81 [C(5)], 128.46 [*C(8)], 128.54 [C(8)], 128.70 [*C(A)], 129.15 [C(3) + *C(3)], 129.43 [C(2') + C(6')], 129.61 [*C(2') + *C(6')], 130.93 [C(7)], 130.97 [*C(7)], 131.24 [C(B)], 131.64 [*C(B)], 132.41 [*C(3') + *C(5')], 132.77 [C(3') + C(5')], 134.50 [C(4)], 138.51 [*C(4)], 141.03 [C(1') + *C(1')], 147.24 [*C(8a)], 147.33 [C(8a)], 150.13 [C(2) + *C(2)].

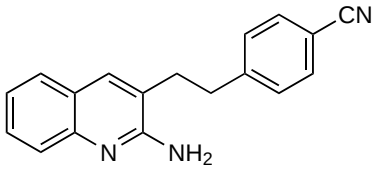
* Denotes signals corresponding to minor *Z*-isomer.

3-(4-(Trifluoromethyl)phenethyl)quinolin-2-amine (143a)



Using General Method 16, **176a** (197 mg, 0.59 mmol) was reacted with 4-methoxybenzylamine (1.5 mL, 11.8 mmol) for 16 hr. The excess reagent was removed by distillation under reduced pressure, and the residue was dissolved in methanol (30 mL) and reacted under an atmosphere of hydrogen with a catalytic amount of Pd-C catalyst for 16 hr. The mixture was filtered through Celite® washing with methanol, and the volatile solvent was removed by evaporation under reduced pressure. The crude residue was treated with TFA (1 mL), and work-up followed by column chromatography on silica gel eluting with 1:19 methanol/dichloromethane yielded **143a** as a white solid (86 mg, 53%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{15}F_3N_2$: 317.1266; found 317.1263. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.84-2.94 [2H, m, H(A)], 3.06-3.16 [2H, m, H(B)], 4.84 [2H, br s, NH_2], 7.26 [1H, dd, $^3J_{5,6} = 8.0$ Hz, $^3J_{6,7} = 7.2$ Hz, H(6)], 7.29-7.34 [2H, m, H(2') + H(6')], 7.50-7.60 [4H, m, H(5) + H(7) + H(3') + H(5')], 7.63 [1H, s, H(4)], 7.66 [1H, d, $^3J_{7,8} = 8.4$ Hz, H(8)].

4-(2-(2-Aminoquinolin-3-yl)ethyl)benzonitrile (143b)



Using General Method 16, **176b** (56 mg, 0.19 mmol) was reacted with 4-methoxybenzylamine (503 μL, 3.9 mmol) for 16 hr. The excess reagent was removed by distillation under reduced pressure, and the residue was dissolved in methanol (30 mL) and reacted under an atmosphere of hydrogen with a catalytic amount of Pd-C catalyst for 16 hr. The mixture was filtered through Celite® washing with methanol, and the volatile solvent was removed by evaporation under reduced pressure. The crude residue was treated with TFA (1 mL), and work-up followed by column chromatography on silica gel eluting with 1:19 methanol/dichloromethane yielded **143b** as a white solid (26 mg, 49%). HRMS (ESI+) $[M+H]^+$ calcd. for $C_{18}H_{15}N_3$: 274.1344; found 274.1338. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.87-2.94 [2H, m, H(A)], 3.08-3.16 [2H, m, H(B)], 4.83 [2H, br s, NH_2], 7.23-7.32 [3H, m, H(6) + H(2') + H(6')], 7.51-7.61 [5H, m, H(4) + H(5) + H(7) + H(3') + H(5')], 7.67 [1H, d, $^3J_{7,8} = 8.3$ Hz, H(8)]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.74 [C(A)], 34.48 [C(B)], 110.55 [C(4')], 118.97 [CN], 121.78 [C(3)], 123.10 [C(6)], 124.41 [C(4a)], 125.78 [C(8)], 127.14 [C(5)], 129.43 [C(7) + C(2') + C(6')], 132.56 [C(3') + C(5')], 136.15 [C(4)], 146.48 [C(1')], 146.70 [C(8a)], 155.87 [C(2)].

Appendix A: Assays of small-molecule ligands with Tec SH3 domain via SPR method.

The Surface Plasmon Resonance (SPR) assays were conducted using a Biacore S200 system, with Biacore S200 Evaluation Software used to display and analyse the assay results.

Protein and sample preparation

GST protein and the GST-SH3 fusion proteins were prepared by Mehrnaz Keyhanfar according to methods previously developed and published.[137] GST protein was used as the reference for the assays to compensate the experimental results for shifts in the bulk refractive index of solutions and for drift, and also to enable identification of non-specific binding events. GST-SH3 fusion protein stocks were in 1 x PBS buffer at concentrations of approximately 1.6 mg/mL. GST protein stocks were in 1 x PBS buffer at concentrations of approximately 1 mg/mL.

The small-molecule ligand solutions were prepared from accurately weighed samples of pure ligand (2-5 mg) dissolved in DMSO to a concentration of 100 mM. The samples were stored in the dark until used to avoid photodegradation. The samples were diluted to 10 mM in DMSO, then to 500 μM in running buffer (1 x PBS, 5% DMSO, 0.05% Tween20).

The sample solutions were diluted to the required assay sample concentrations into GE Healthcare Life Sciences 96-well microplates using a Hamilton MicroLab Nimbus96 (enclosed) pipetting robot.

Immobilisation onto sensor chip

The running buffer used during the immobilisation process was 1 x PBS with 0.05% Tween20.

The sensor chip surfaces were preconditioned with two successive injections of each of the preconditioning solutions: 50 mM NaOH, 10 mM HCl, 0.1% SDS, 0.85% H_3PO_4, and 50 mM glycine (pH = 9.5).

The sensor chip surfaces were activated by injection of a 1:1 mixture of NHS and EDC (100 μL each) at a flow rate of 10 μL/min over 900 seconds. The protein was diluted to approximately 1 μM with 10 mM sodium acetate solution (pH 5.2) and injected across the surface at a flow rate of 2 μL/min. Protein injections were repeated until response increases were not observed upon injection of more protein, indicating saturation of surface. An typical increase in the response of approximately 6000-8000 Response Units (RU) was observed at this step.

The remaining active NHS esters were blocked with two successive injections of 1.0 M ethanolamine (pH 8.5) at a flow rate of 10 μL/min (2 x 210 seconds); a small decrease in RU was observed as a result.

The final amount of immobilised protein was determined as the difference in RU between activation and blocking steps. Similar amounts of immobilised GST protein and GST-SH3 fusion protein were achieved.

Screening method

The running buffer used for the assay runs, including injection of small-molecule ligands, was 1 x PBS with 5% DMSO and 0.05% Tween20.

The addition of 5% DMSO in the running buffer and solutions assisted with solubility of the small-molecule ligands. Solvent correction was required to compensate for the bulk refractive index shift due to addition of DMSO. The solutions used for the solvent correction were 5.8-4.5% DMSO solutions in 1 x PBS with 0.05% Tween20.

Nine concentrations of each ligand (including a blank) were screened for binding with the GST (reference) and GST-SH3 fusion protein. For screening, the concentrations tested are shown in Table A-1.

Table A-1: Concentrations of small-molecule ligands used for screening assays.

Compound screening concentrations (μM)
0
0.78125
1.5625
3.125
6.25
12.5
25
50
100

A run of assays typically contained 10 small-molecule samples. For each run of assays, a series of start-up cycles was followed by sample correction samples before assays of small-molecule compounds. Solvent correction was repeated after 6 small-molecule compound runs for consistency.

Data evaluation

The solvent correction samples were used to generate a calibration curve to correct for the effect of the solvent upon the response measured (Figure A-1), and this correction was then applied to all samples in the assay run to compensate for the DMSO bulk shift.

Reference subtraction and correction (using the GST reference samples) was applied to each set of data.

The baselines before injection of small-molecule compound were overlaid (i.e. RU set to zero) for each sensorgram to account for any loss of active protein on the sensor surface.

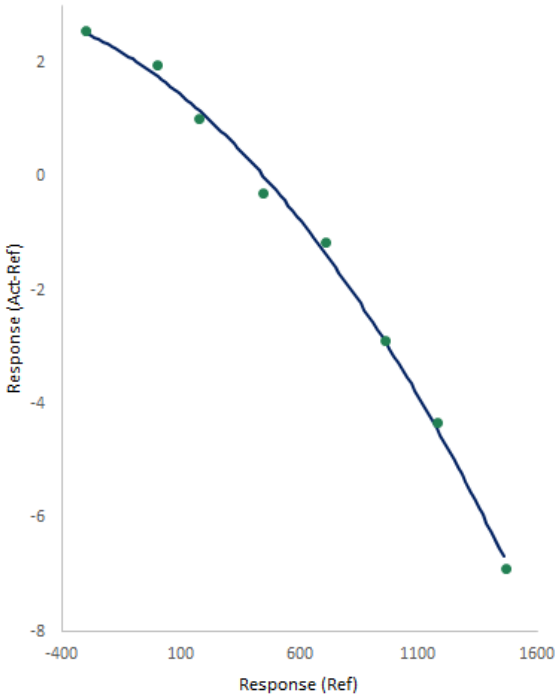


Figure A-1: Example of solvent correction applied in assay runs to compensate for shift in bulk refractive index due to addition of DMSO. For each solvent correction solution (5.8-4.5% DMSO), the relative response difference upon sample injection was measured for the GST-SH3 fusion protein surface (Response (Act-Ref)) and the reference GST protein surface (Response (Ref)), and these data points were plotted to generate the solvent correction curve.

The resulting sensorgrams for each concentration were overlaid. Visual inspection determined if the sensorgrams appeared stable over time. A report point was selected (6 seconds prior to end of sample injection) in the region of equilibrium binding. The response around a five second region of the report point was averaged, and this response was used as a measure of the response at equilibrium binding (see Figure A-2).

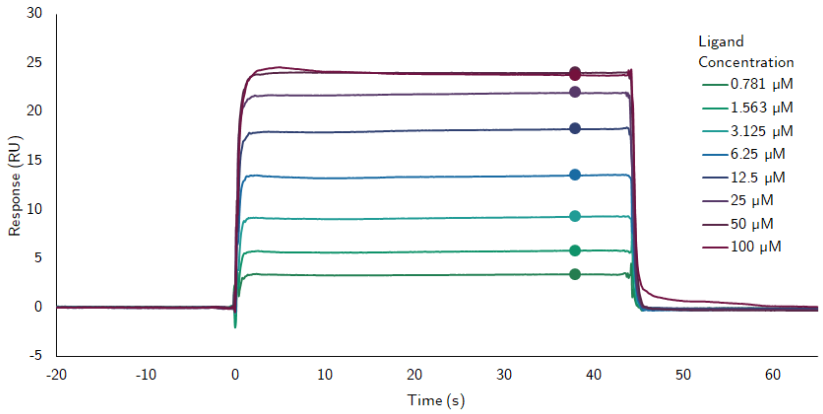


Figure A-2: Example of assay sensorgrams and selected report point. Example shown is for **22a**.

Affinity evaluation

For each concentration of small-molecule ligand, the response at the report point for equilibrium

binding (R_{eq}, in RU) was plotted against the concentration (C, in μM). Using the software, a steady-state affinity curve was fitted to the data according to the following equation for a 1:1 binding interaction:

$$R_{eq} = \frac{C.R_{max}}{C + K_d} + RI \quad (3)$$

The curve fitting process used nonlinear regression analysis to fit the K_d value, R_{max}, and RI using the initial values shown in Table A-2, giving a binding isotherm which minimises the χ^2 value (Figure A-3).

Table A-2: Fitted values determined by nonlinear regression analysis.

Fitted value		**Initial value**
K_d	Equilibrium dissociation binding constant	0.1 x maximum concentration of ligand assayed
R_{max}	Maximum response, at saturation of protein binding sites	maximum response measured for assays
RI	offset due to bulk shift during injection	0.2 x maximum response measured for assays

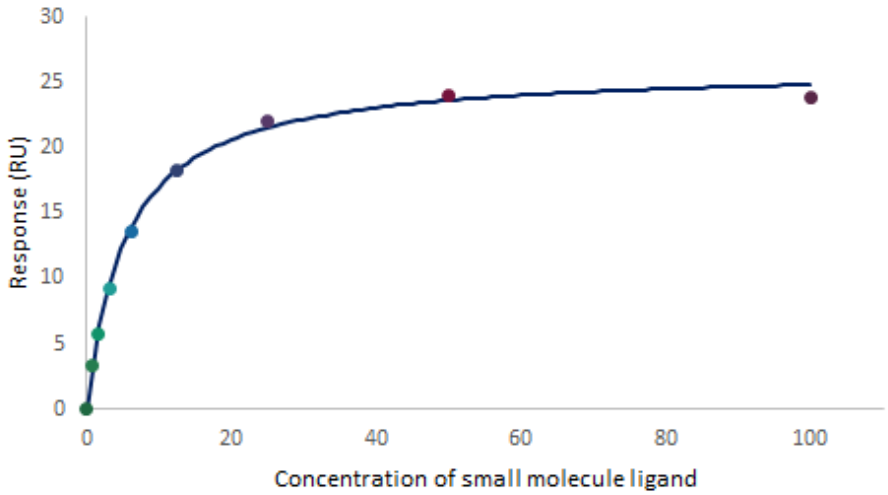


Figure A-3: Example of steady-state affinity analysis used to determine the K_d value. Example is for **22a**.

Affinity evaluation K_d value for strongest binding ligands.

For small-molecule ligands where the screening K_d value was comparable or better than the previous lead compound (i.e. K_d value < 10 μM) the assays were repeated in triplicate. The range of concentrations tested was generally adjusted to appropriately cover the measured K_d value, ideally using a maximum concentration approximately 10 x the K_d value. This concentration typically ensured that sufficient data points were below and above the K_d value to avoid extrapolation and minimise error, and that the higher concentrations were close to saturation of the protein binding sites, to avoid extrapolation of the R_{max} value.

The mean and standard deviation were reported for the K_d values determined by the SPR assays if at least three assay measurements were collected.

Affinity evaluation for ligands with atypical assay results

In some cases, atypical or inconsistent response measurements meant that the sensorgrams for each tested concentration of the screening assays could not be effectively used to determine the K_d value. This was typically due to poor solubility, stability, or aggregation of the small-molecule ligand at higher concentration, which resulted in a decrease in RU observed at higher concentrations where saturation of protein binding had been achieved at lower concentrations. In cases where the response values significantly decreased at higher concentrations (for example, see Figure A-4), using these concentrations in the affinity evaluation results in a significant underestimate and error in determination of the K_d value. In these cases, the highest concentrations where reduced binding were removed from the affinity evaluation and noted.

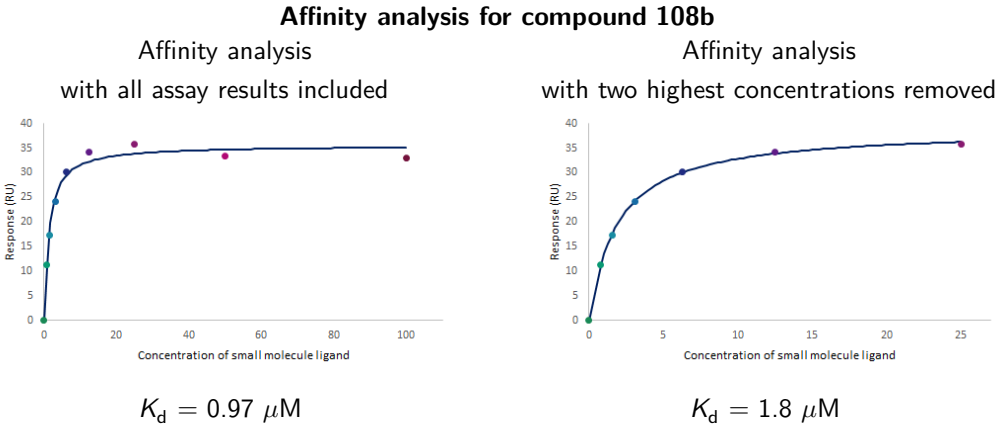
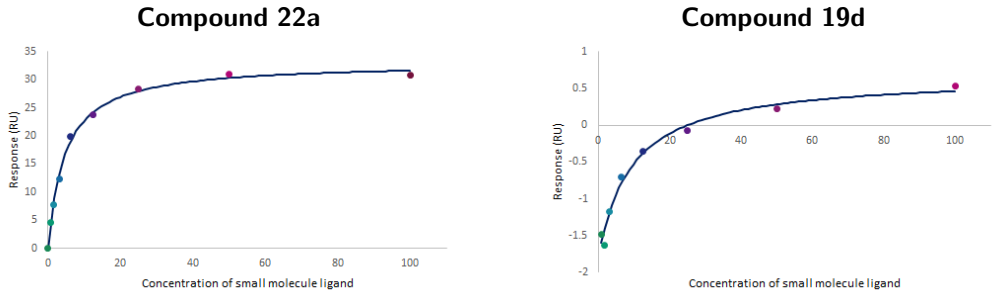


Figure A-4: Example of anomalous behaviour affecting accuracy of results for some concentrations in the SPR screening assays. Including all concentrations in the affinity analysis results in underestimate of K_d value.

For the stronger binding ligands (such as **108b** in Figure A-4), saturation binding was achieved at significantly lower concentrations, so in the follow-up replicate assay lower concentrations were used to obtain a better measurement of the K_d value. In cases where the response-concentration curve did not appear to be reaching the saturation binding plateau, this was

also indicated in the results as it may result in an increased error in the fit of the data.

In some cases low response values were observed. The compound **22a** was used as a standard in every assay run and gave consistent responses and calculated K_d values. Assays of some small-molecule ligands had negligible response compared to the standard compound, which could be due to weak interaction (or no interaction) with the protein surface or insolubility of small-molecule ligand. In either case, the low response was noted. In some cases the affinity analysis could still be used to calculate a 'K_d value' despite the low response (for example, see Figure A-5), however this calculated value does not accurately reflect the strength of the protein-ligand binding interaction. The K_d value refers to the concentration of ligand required to occupy half of the saturation binding sites of the protein target, and therefore if the response is too low for saturation binding then the data cannot be used to determine the K_d value. For this reason, assays results for ligands which gave low responses compared to the standard **22a** were not considered comparable, and therefore affinity analysis was not pursued further.



R_{max} = 34 RU
K_d = 4.4 μM

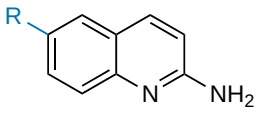
R_{max} = 2.5 RU
K_d = 9.4 μM

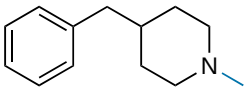
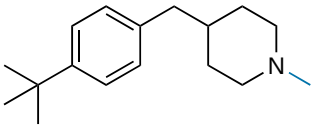
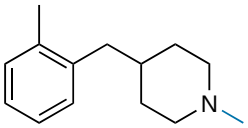
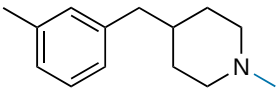
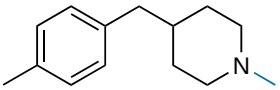
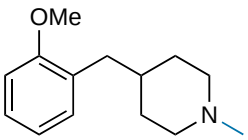
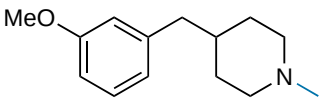
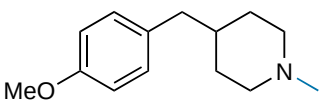
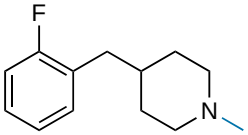
Figure A-5: Example of low response binding, giving results which are not representative of strength of binding interaction. Response-concentration curves for the standard compound (**22a**) and weakly binding sample **19d** for the same assay run. Even though a curve can be fit to data for **19d**, the low response compared to **22a** demonstrates saturation binding was not achieved and therefore the calculated K_d value is not indicative of the binding affinity.

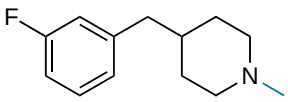
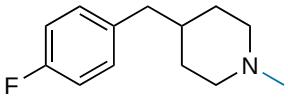
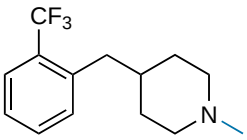
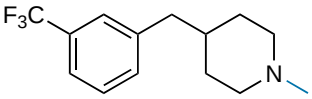
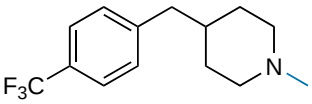
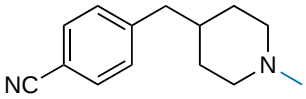
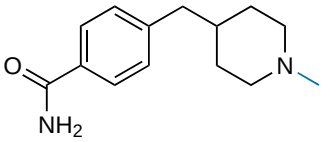
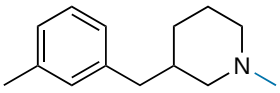
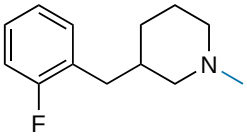
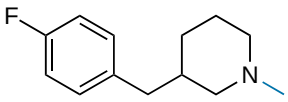
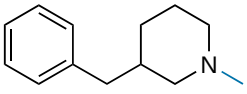
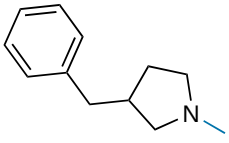
Appendix B: Summary of SPR assay results for extended 2-aminoquinoline derivatives with Tec SH3 domain.

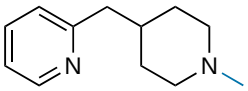
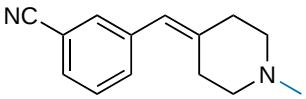
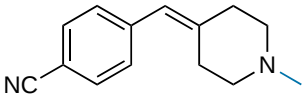
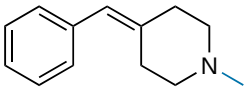
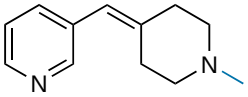
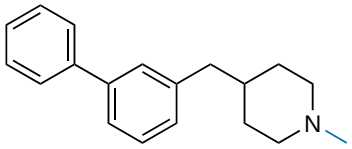
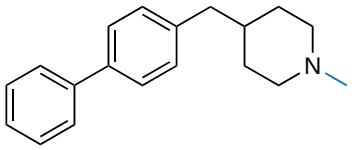
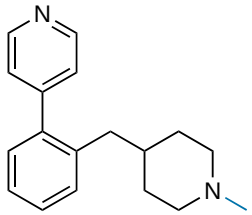
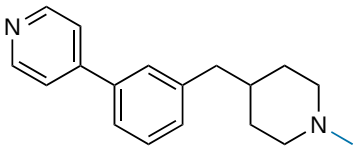
6-Position extended 2-aminoquinoline ligands

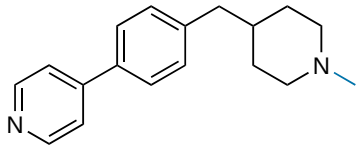
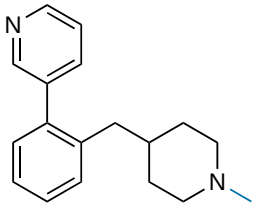
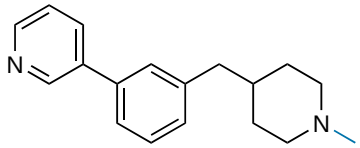
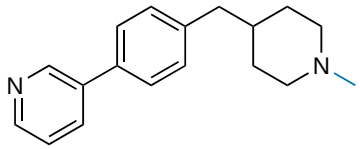
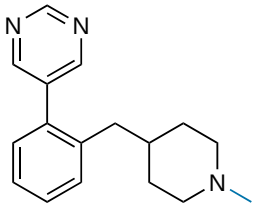
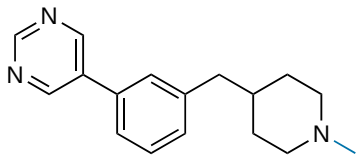
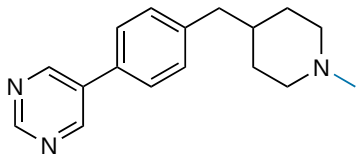
Table B-1: Results of SPR assays for 6-position substituted 2-aminoquinoline ligands.



R =	Compound	Screening K_d (μM)	Assay $K_d \pm$ SD (μM)
	**15**	9.1	27 ± 11^{b}
	**19a**	*insoluble*	
	**19b**	29.3^{b}	
	**19c**	$> 50^{b}$	
	**19d**	9.4^{c}	
	**19e**	$> 20^{b}$	
	**19f**	$23.7^{a,b}$	
	**19g**	15.4^{b}	
	**19h**	17.8^{c}	

R =	Compound	Screening K_d (μM)	Assay $K_d \pm$ SD (μM)
	**19i**	13.2	
	**19j**[c]	13.9[c]	
	**19n**	> 30[b,c]	
	**19o**	> 30[b]	
	**19p**	> 50[b,c]	
	**19s**	1.7[a]	2.0 $\pm$ 0.5
	**101**	1.9[a]	2.0 $\pm$ 0.1
	**20c**	16.4	
	**20h**	5.2[a,b]	19 $\pm$ 7[a,b]
	**20j**	20.6[a,b]	
	**20x**	13.0	
	**21x**	9.6	9.7 $\pm$ 0.3[a]

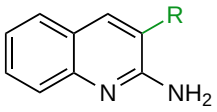
R =	Compound	Screening K_d (μM)	Assay $K_d \pm$ SD (μM)
	**22a**	5.8	5 ± 1
	**102r**	16.7	
	**102s**	2.9	2.2 ± 0.7
	**102x**	9.0	20 ± 3
	**108b**	1.5[a]	1.9 ± 0.1
	**113a**	*insoluble*	
	**113b**	*insoluble*	
	**114a**	5.4	6 ± 3[a]
	**114b**	*insoluble*	

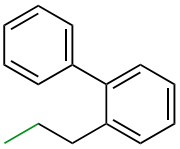
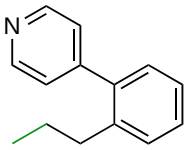
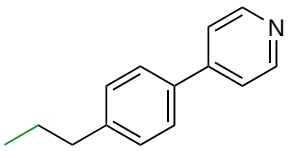
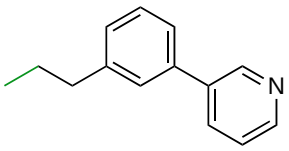
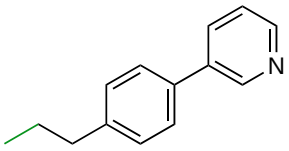
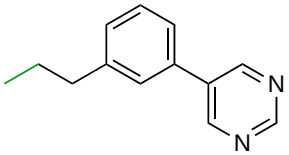
R =	Compound	Screening K_d (μM)	Assay $K_d \pm$ SD (μM)
	**114c**	*insoluble*	
	**115a**	13.9	10 ± 4
	**115b**	> 20	
	**115c**	5.2	7 ± 4[a]
	**116a**	9.3	7 ± 1[a]
	**116b**	7.9	4.1 ± 0.7[a]
	**116c**	3.2	2.4 ± 0.2

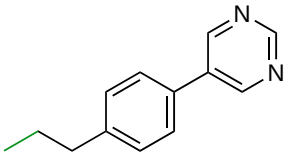
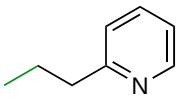
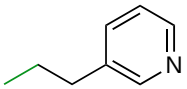
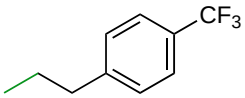
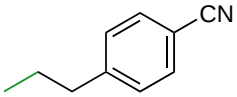
[a] Highest concentration data point removed due to precipitation or aggregation of compound under assay conditions. [b] Response-concentration curve not at plateau, saturation binding not achieved. [c] Response too low for saturation binding.

3-Position extended 2-aminoquinoline ligands

Table B-2: Results of SPR assays for 2-aminoquinoline ligands with a 3-position biaryl substituent.



R =	Compound	Screening K_d (μM)
	**138a**	*insoluble*
	**139a**	$> 50^a$
	**139b**	$> 50^a$
	**140a**	$> 50^a$
	**140b**	$> 50^a$
	**141a**	$> 50^a$

R =	Compound	Screening K_d (μM)
	**141b**	$> 50^a$
	**142a**	$> 50^a$
	**142b**	$> 50^a$
	**143a**	*insoluble*
	**143b**	$> 50^a$

[a] Response-concentration curve not at plateau, saturation binding not achieved.

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